THE IMPACT OF EPILEPSY ON THE MATERNAL AND FOETAL OUTCOME

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CERTIFICATE

This is to certify that this Dissertation entitled, **"THE IMPACT OF EPILEPSY ON THE MATERNAL AND FOETAL OUTCOME"** is a bonafide record of work done by **Dr. N. THAMILPAVAI,** under our guidance and supervision in the Institute of Neurology, Rajiv Gandhi Government General Hospital, Madras Medical College, Chennai, submitted as partial fulfillment for the requirements of D.M. Degree examination Branch-I NEUROLOGY, AUGUST 2013, under the Tamil Nadu Dr. M.G.R. Medical University, Chennai.

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DECLARATION

I solemnly declare that this dissertation titled **"THE IMPACT OF EPILEPSY ON THE MATERNAL AND FOETAL OUTCOME"** is done by me in the Institute of Neurology, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai under the guidance and supervision of **Prof. Dr. K. BHANU, Dip. NB., D.M.,** Professor of Neurology, Institute of Neurology, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai. This dissertation is submitted to the Tamil Nadu Dr. MGR Medical University, Chennai in partial fulfillment of the university requirements for the award of the degree of D.M. Neurology.

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CONTENTS

ABBREVIATIONS

WWE	-	Women With Epilepsy
PCOS	-	Poly Cystic Ovarian Syndrome
TLE	-	Temporal Lobe Epilepsy
AED	-	Anti Epileptic Drugs
GTCS	-	Generalized Tonic Clonic Seizures
CPS	-	Complex Partial Seizures
SPSWSG	-	Simple Partial Seizures With Secondary Generalization
CPSWSG	-	Complex Partial Seizures With Secondary Generalization
CVT	-	Cortical Vein Thrombosis
PHT	-	Phenytoin
CBZ	-	Carbamezipine
PB	-	Phenobarbitone
SVP	-	Sodium Valproate
LV	-	Levetiracetam
OXC	-	Oxcarbazepine
LTG	-	Lamotrigine
MCM	-	Major congenital malformation
ASD	-	Atrial septal defect
VSD	-	Ventricular septal defect
TOF	-	Tetralogy of Fallot
PDA	-	Patent ductus atreriosus
CHPS	-	Congenital hypertropic pyloric stenosis
EA	-	Esophageal Atresia

INTRODUCTION

Epilepsy is the commonest neurological disorder seen in clinical practice. The incidence of epilepsy is 44 per 100,000 person years. The incidence in females, is 41 per 100,000 person years, and for males is 49 per 100,000 person years. [1,2] The prevalence of epilepsy was slightly higher in males than females (6.5 vs 6.0 per 1000 persons) in the epileptic study reported at Rochester. In India people affected by epilepsy are more than 10 millions, constituting a prevalence of about 1% of the population. There are 2.73 million women with epilepsy in India and about 52% of them are in the reproductive age group.

EFFECTS OF HORMONE ON EPILEPSY

Epilepsy can occur in women during any part of their lifetime, either at puberty, pregnancy or menopause. Epilepsy in women is affected by a number of factors. Sex differences and the effects of steroid hormones, such as androgens, estrogens, and progestogens, influence seizures [3]. Early organizational and later activational effects of these hormones can amplify sex/gender differences in the expression of some seizure disorders which are modulated by androgen. Estrogens can activate seizures and interictal discharges when directly applied to the cerebral cortex or infused intravenously. Estrogen acts as a glutamate agonist in the hippocampus and its actions are mediated due to altered calcium permeability of the cell membrane,

and reduction of chloride influx through the gamma-aminobutyric acid (GABA)-A receptor. Progesterone decreases cortical excitability, by enhancing GABA effects, and increases electroshock seizure threshold in experimental models.

Cortical excitability is also known to be affected by pituitary and gonadal hormones. An marked increase in pituitary luteinizing hormone (LH), follicle-stimulating hormone (FSH),and their cyclic fluctuations,occurs with the onset of menarche. They also fluctuate during pregnancy, the perimenopausal period, and with the introduction of oral contraceptives, and hormone replacement therapy. This hormonal increase occuring during menarche, contributes to the onset of epilepsy during this period . There is marked interindividual variability in response to these hormonal alterations resulting in changes in epilepsy and seizure threshold. Seizure types are exacerbated by different hormonal patterns

Catamenial epilepsy is due to exacerbation in seizures with the onset of menstrual cycle.[3,4] True catamenial epilepsy requires reproducible and consistent increase or change in character of seizures at the same point in a regular menstrual cycle. Anovulatory cycles can make the relationship of seizure to hormones difficult to discern. Epilepsy expressed at this time may in part due to this increase in estrogen, or cyclic increases in estrogen relative

to progesterone which appear to act as a likely trigger for breakthrough seizures.

PREGNANCY HORMONAL ALTERATIONS

There is a marked increase in the levels of estrogen and progesterone as well as an alteration in the metabolism of hormones and antiepileptic drugs.[3]

Menopause may occur earlier in women with epilepsy than in the general population. Onset of menopause was earlier in women with a high seizure rate.[5] Seizures may disrupt the hypothalamic pituitary function or alter neutrally mediated trophic effects on the ovary.

Infertility

Women with epilepsy show reduced fertility in comparison with women in the general population. At least one third of menstrual cycles in women with generalized seizures are anovulatory. PCOS ,or hypothalamic amenorrhea has been found in 12.5% of women with TLE whereas it occurs in 1.5% of general population. [3]

EFFECTS OF EPILEPSY ON THE HORMONES

Fluctuations in the levels of luteinizing hormone (LH) and pulsatile release of prolactin and sex steroids have been observed in temporal relation to some seizures. [6]

The type of epilepsy may also have a significant influence on reproductive hormones and function. The temporal limbic system plays a vital role in reproductive endocrine regulation and in sexual function .In patients with medial temporal lobe epilepsy there is disruption of the hypothalamic pituitary axis and altered gonadal function.[6]

Anti-epileptic drugs (AEDs) enables 60% of them to remain seizure-free, another 20% to achieve partial control of seizures, but the remaining 20% are unresponsive to AEDS .Pregnancy influences seizures by causing an increase in seizure frequency in one fourth, decreases in another one fourth, and no change in the seizure in the remaining half. Each and every pregnancy, even under excellent, care is risky at times. Most patients are unwilling to accept the side effects of antiepileptic drugs, due to fear and misperceptions about the facts related to pregnancy, epilepsy, and antiepileptic drugs Therefore it is the prime duty of every doctor treating women with epilepsy(WWE) who are planning to become pregnant or having become pregnant to explain the risks associated with the disorder and the drugs used for treatment .Patients should be ensured that they can be ensured a safe pregnancy and delivery by stringent care and monitoring.

Patients must be informed that untreated seizures by themselves may increase the risk of birth defects by (Annegers et al.) [7] who also separated the effects of AEDs from those of seizures during pregnancy. Patients should

be made aware of the fact that under the best of circumstances,any pregnancy may carry a 1-2% risk of having an offspring with a malformation and that, the mother with a seizure during pregnancy may double that risk. [7]

Many patients are aware that AED usage during pregnancy increases the risk of malformations and it is not uncommon for patients to stop the AEDs as they plan their pregnancy. Clinical experience and circumstantial evidence suggest that WWE who have uncontrolled seizures during pregnancy have a significantly increased (up to tenfold) morbidity and mortality as compared to the general population.[8,9] Patients should be advised that stopping AEDs treatment prior to pregnancy is harmful to both the mother and child in those presenting with active seizure disorder.

Most of the WWE, will require long term treatment with antiepileptic drugs (AEDs) to prevent seizures. Though the interactions between epilepsy and pregnancy are multiple, it is the untoward effect of AEDs on the developing fetus that is a cause of major concern to the child bearing individual.

REVIEW OF LITERATURE

EFFECTS OF PREGNANCY ON EPILEPSY.

Approximately 1.1 million women with epilepsy are of child bearing age group. Preconception counseling is necessary for women with epilepsy and is a time to educate and inform these patients about optimal care before, during, and after pregnancy. It should be acknowledged that once women reaches the reproductive age that pregnancy is possible, whether planned or not, and preconception counseling should be done very frequently during routine neurological visits.

Pregnancy in WWE is associated with increased maternal risks and adverse neonatal outcomes compared to the general population. Concensus guidelines by the American academy of neurology [25] has emphasized minimizing the associated risks by reducing the AED dosage and by folic acid intake.But there are no guidelines regarding the best management once a women is pregnant.

SEIZURES IN PREGNANCY

The assessment of a women's seizure activity is imperative when considering reproductive options. [10,11] It is recognized that seizure activity increases in pregnancy in about a quarter , has no change in about a half.

Investigators evaluating the course of epilepsy during pregnancy have shown an increase in 24%[12], a decrease in 23%, and no change in 53%. Recent studies by (Vadja et al) [13] has shown that being seizure free prior to pregnancy is associated with seizure freedom during pregnancy. The risk for status epilepticus during pregnancy is about 1-2%. Status epilepticus is known to cause increased risk of maternal morbidity and mortality and fetal mortality in older studies but this risk appears to be substantially lower with improvements made in treatment (EURAP Study Group). [14] Seizures during pregnancy imposes risk to both the mother and fetus, convulsions may cause lactic acidosis and transient increase in uterine pressure and blood flow. It is recommended for the patient to be placed in the left lateral decubitus position to facilitate fetal blood flow and reduce the possibility of aspiration Barrett and Richenset al. [15]

The onset of structural and metabolic changes may precipitate new onset seizures during pregnancy. Changes in the pattern of seizure occurrence would include structural causes like intracranial hemorrhage, cerebral venous sinus thrombosis, and ischemic stroke, hyperemesis gravidarum, acute hepatitis (due to fatty liver of pregnancy or viral hepatitis) metabolic disorders such as acute intermittent porphyria ,infections like malaria and gestation induced hypertension.

Risk for deterioration in seizure control has been associated with focal onset epilepsy, polytherapy, monotherapy with oxcarbazepine [OXC] or lamotrigine [LTG], and poor compliance associated with lack of prepregnancy planning. [14,15] There is intraindividual variability in patterns of seizure control in successive pregnancies, and interindividual variability among WWE. [16]

During pregnancy, AED dose may require an modification, an increase in some patients, if free drug levels fall, or if the semiology of seizures changes. It is important to maintain good compliance with AEDs throughout pregnancy to avoid relapse of seizures, especially because some patients may discontinue AEDs due to a perceived risk, by themselves without discussing it with their treating physicians. [14]

Seizures are most likely to occur in the first trimester and in the peripartum period. Nearly 5% of WWE, will have peripartum seizures, representing a three-fold increase compared to the rest of pregnancy. This is due to factors such as poor compliance, dehydration, decreased oral intake, and intercurrent medications. [12,14]

Factors influencing seizure control during pregnancy

Gestation induced alteration in AED pharmacokinetics

Knowledge of the pharmacokinetics of the different AEDs during pregnancy is necessary for the treating physician to appropriately anticipate and implement necessary medication changes (Perucca). [6,15,17] A major factor is decreased binding to plasma proteins,which causes lower total plasma levels, but generally free (unbound) and active drug concentrations remain stable.

PHYSIOLOGICAL CHANGES DURING PREGNANCY: ITS EFFECTS ON DRUG DISPOSITION

PARAMETERS	CONSEQUENCES
↑Total body water extracellular fluid	Altered drug metabolism
↑ Fat stores	↓ Elimination of lipid soluble drugs
↑Cardiac output	↑Hepatic blood flow leading to ↑ elimination
↑Renal blood flow and glomerular flow rate altered CYP 450 activity and UGT activity	↑Renal clearance of unchanged drug,altered systemic absorption andhepatic elimination
↓Maternal albumin	Altered free fraction,increased availability of drug for hepatic excretion.

Psychological

- Noncompliance with medications.
- Increased stress and anxiety.

Physiologic

- Sleep deprivation

Hormonal

- Increased estrogen / progesterone ratio
- Increased human chorionic gonadotropin levels in first trimester

Battino et al [18] found that total and unbound plasma concentrations of Phenobarbital decline throughout pregnancy by nearly 50% .Yerby et al. [19] reported no significant changes in free valproate levels, although total levels declined significantly. They also reported a 42% decrease in total plasma carbamazepine levels along with a 22% decrease in free carbamazepine. However, Tomson et al [15] found much less reduction in levels. Both these groups found a 40% decrease in total phenytoin levels and a 20%decrease in free levels.

Levels of newer AEDs like lamotrigine are dramatically affected during pregnancy.By the 32nd week of gestation, clearance may increase more than threefold (Pennell et al; Tran et al.)[20,21] There is a greater decrease in drug levels compared to older AEDs and may cause increased seizure frequency or

severity, which can prevented by escalating doses. If raised during, pregnancy, the dose needs to be reduced after delivery, to reduce postpartum toxicity .The pharmacokinetics of the other newer AEDs on the course of pregnancy is not very clear.

PERIPARTUM SEIZURES

EFFECTS ON THE MOTHER

Three percent of women with epilepsy are at risk of developing seizures at delivery and in the next following 24 hours.This may be due to failure to take AEDs, lack or inadequate sleep, or impaired drug absorption. Women with generalised epilepsies are at increased risk during or immediately after delivery, than those with partial siezures if the AED concentrations are maintained sub-therapeutically due to inadequate drug dosage. Status epilepticus is associated with high a maternal and infant mortality and should be managed aggressively. Prophylactic use of clobazam is advocated during peripartum period.

PLACENTAL FACTORS AFFECTING AED TRANSPORT

In case of placental transfer there is an increasing awareness of drug transporters or efflux proteins that regulate AED passage into the fetal circulation. Placental drug transporters have increased blood brain barrier expression especially in those with refractory epilepsy. Though the placenta expresses many CYP 450 (including CYP1A1,2E1,3A4,3A7,4B1) and uridine

diphosphonate glucoronyl transferase isoenzymes, AED excretion via this route minimally affects the foetus

Transporters like MDR I , multidrug resistance protein 1 and 2 (MRP 1, MRP 2), and monocarboxylate transports are located at the apical membrane of the syncytiotrophoblast where they extrude drugs from the fetal circulation back into the maternal one (Atkinson et al ; Syme et al.)[22,23]

EFFECTS ON THE INFANT

Some AEDs like primidone, phenobarbitone, and the benzodiazepines, are sedating and few infants manifest drug withdrawal symptoms in the first few days of neonatal life. Withdrawal seizures are rare, but are said to be most common with phenobarbitone.

PROBLEMS IN FEEDING AND DRUG WITHDRAWAL

Virtually all AEDs are excreted in breast milk, but only in low concentrations. The amount of drug received by the infant is less than that what the fetus receives during pregnancy. The higher the protein binding capacity of the AED, the least will be transferred from plasma to breast milk. The elimination half-life of most of the AEDs tends to be prolonged in neonates.

Breast feeding should be encouraged in all women with epilepsy taking AEDs.. Newer drugs and drugs like LTG, PHT, PB, primidone[24,25] should be

introduced with great care in the postpartum period to breast feeding women as they are excreted in the breast milk. For the AEDs ethosuximide, levetiracetam, Lamotrigine, and zonisamide, there is a potential for significant breast milk concentrations, however there are no safe guidelines on whether lactation is safe. In these circumstances the lowest dose of AED to achieve seizure control is given, and the mothers are advised to report any excessive, sedation, irritability, feeding difficulty ,or failure to gain weight. If this occurs then formula feeds are instituted,or discontinuiation of lactation is needed..

EPILEPSY IN THE POSTPARTUM PERIOD

Mothers with uncontrolled epilepsy should not be left alone with babies, for it presents a greater risk to infants and toddlers than to the fetus.The infant may drop down from the mother' s hand at the start of the seizure if left unattended, more common in juvenile myoclonic epilepsy patients.They should be carefully supported by family members during all activities of the mother, even during nursing and bathing of babies. Dosage adjustments of AEDs should be done in the postpartum period if they were increased during antenatal period.

EFFECTS OF EPILEPSY ON PREGNANCY

The data from Indian epileptic registry from kerala by Sanjeev Thomas et al [26,27] reported an increased incidence of, spontaneous abortions as more common in epileptic women. Borthenet al from Norway found that epileptic

pregnant women consuming AEDs had a 1.5-fold increased risk of mild preeclampsia, two-fold increased risk of late vaginal bleeding, a 1.5-fold increased risk of gestational hypertension and delivery before week 34 weeks of gestation. Epileptic pregnant women not on AEDs had no increased risk of antenatal complications compared to the general population. A recent study showed that carbamazepine in particular was associated with a higher risk for pre-eclampsia. AED-induced folate deficiency and alteration in the metabolism of vitamin K-dependent blood clotting factors have been suggested as possible causes of vaginal bleeding in late pregnancy.

OBSTETRICAL RISKS AND MANAGEMENT DURING LABOUR

For the most part, patients with seizure disorders do well in pregnancy. Richmond et,al [28] reported on 414 births from 314 women from 1978 to 2000 with seizure disorder, found an increased risk for nonproteinuric hypertension, and induction of labour they found that these patients had fewer instrumental vaginal deliveries. Less than one antenatal seizure did not have an effect on antenatal outcome if treated appropriately. There was no difference in other complications of pregnancy and only a small increase in caesarean section rates.

Studies have shown a clearly increased risk of caesarian section in WWE Pilo et al; [29] and no studies show an absence of increased risk. The

overall risk is around twofold; however, the reason for the increased caesarian-section rate is unclear.

Patients with epilepsy should be followed up closely for signs and symptoms of pregnancy complications besides having their antiepileptic drug serum concentrations monitored serially throughout pregnancy. For example, serial growth scans are done to rule out growth abnormalities such as intrauterine growth retardation, congenital abnormalities, placental insufficiens, and to assess the adequacy of amniotic fluid. Blood pressure should be monitored frequently for signs and symptoms of preeclampsia. Likewise, they should be watched for signs and symptoms of preterm labour.[27]

EFFECT OF EPILEPSY ON THE FOETUS

The untoward effects of epilepsy and AEDs on the fetus are (1) anthropometric changes, (2) physiological changes, (3) teratogenic effects, and (4) long-term cognitive effects. [9] Several studies have shown that infants of WWE have low birth weight and are small for gestational age. A large population-based study in Norway had shown that infants of WWE exposed to AEDs in utero had higher risk of preterm birth, low birth weight, intrauterine growth retardation, and smaller head circumference at birth. Similar findings in birth weight were observed in neighboring Sweden also.[30] Head circumference at birth in infants of WWE is influenced by the paternal head

circumference, maternal AED exposure and several other factors. Apgar score at birth is a reliable measure of the physiological status of the newborn. Population-based studies in Norway had revealed that infants exposed to AEDs in utero of mothers with epilepsy had lower Apgar score than the controls.

MALFORMATIONS

The occurrence and degree of an abnormality (i.e., deviation from the norm) bear close relationship with time of exposure, the "critical period." Insults at very early stages of development (first few hours or days) are more likely to affect primordial cell lines responsible for organogenesis and result in significant abnormalities or absence of all its derivatives. These are more often lethal defects.

In neurological parlance, the " anatomic critical period " is the time of occurrence of a given malformation (i.e., neural tube defects occur between 30 and 31 days).The practice of stopping AEDs by the second or third weeks of pregnancy to prevent early malformations is usually not recommended because of the potential to increase the risk of seizures. All pregnant patients should be made aware of these facts and any concerns about AED-induced malformations should be addressed prior to pregnancy.

Major congenital malformations(MCM) are defined as a physical defect requiring medical or surgical intervention and causing major functional disturbance. Minor malformation do not require any treatment and not life threatening.

System	Malformations
CVS	TOF, ASD, VSD, PDA, PA, Single ventricle
Craniofacial	Cleft lip, cleft palate
Skeletal	Club foot, hip dislocation, etc.
CNS	Neural tube defects
GIT	EA, CHPS, omphalocele, hernia (diaphragm, inguinal, umbilical)
GUT	Renal agenesis, hydronephrosis, hypospadias, undescended testes
Others	
Total	

Congenital malformations can affect any organ and the risk is doubled in epileptic women by Vadja et al, Holmes et al, meador et al. [31,32,33]

Developmental delay and cases of fetal anticonvulsant syndrome, where there was a combination of dysmorphic features but no major defects as defined above were coded as minor structural malformations, although they were significant defects in themselves.

There is an increased risk of malformation in WWE exposed to AED, than in those whom are not exposed. [33,34,37,38]

Antiepileptic treatment and incidence of major congenital malformations

DRUG USAGE	INCIDENCE OF MAJOR CONGENITAL MALFORMATIONS
Any antiepileptic drug	7.86%
Lamotrigine monotherapy	2.1%-2.9%
Carbamazepine monotherapy	2.0%-5.2%
Phenobarbital monotherapy	4.7%-6.5%
Phenytoin monotherapy	3.4%-10.5%
Valproic acid monotherapy	8.6%-16.7%
Untreated	0.8%-5.0%
General population	1.62%-2.2%

LATE EFFECTS DUE TO LATE EXPOSURE

Susceptibility to developmental abnormalities is not limited to the first trimester of pregnancy. The central nervous system continues to grow and changes continue during pregnancy. Agents that interfere with neurocognitive development can do so throughout that period. In some cases, the neurocognitive disorders can be as devastating as a malformation, on children and families. SVP, PB, and Primidone can have adverse effects on CNS development (Adab et al.; Meador et al.,) [47,35] Clinically,they are manifested as small head circumference and attentional and learning deficits that may go undetected until school years. Given the potentially serious cognitive implications and the uncertainties in ascertaining causation, the use of valproic

acid, phenobarbital, and primidone should,if at all possible, be avoided throughout the duration of pregnancy.

EFFECTS ON AEDS ON LACTATION FETAL AND NEONATAL EXPOSURE

Epileptic pregnant women can have healthy babies even with significant placental exposure and can breast feed their babies safely with cautions. Phenobarbital and primidone should be avoided in parents wishing to breast feed. Significant breast milk concentrations are found to occur for. the AEDs ethosuximide, levetiracetam, lamotrigine, topiramate and zonisamide; however, there are no firm guidelines on whether lactation is safe.[24]

Indirect neonatal anticonvulsant exposure comes from certain situations. First involuntary exposure occurs in utero through transplacental transfer in mothers receiving anticonvulsants. The second is through ingestion of breast milk containing anticonvulsant in mothers with epilepsy.

FACTORS INFLUENCING ANTICONVULSANT DISTRIBUTION TO THE NEONATE

Many of the factors that determine placental and breastmilk transfer are similar. The most common means by which drugs reach the neonate is by passive diffusion. In such instances, the amount of drug that crosses a membrane per unit of time is dependent on the difference in concentration of

drug in the maternal and fetal or neonatal circulations, its physiochemical properties, and the rapidity of maternal drug clearance. Lipid soluble,un-ionized drugs with low molecular weights (less than 500Daltons) tend to diffuse more readily andrapidly. Most AEDs tend to be either weak acids or weak bases; therefore the drug's pka and maternal/neonatal blood ph ratio affects its relative ionization.

Because it depends on maternal diet, the extent of transfer can vary across the course of a day or between days. AEDs with greater lipid solubility tend to distributed more rapidly into breast milk. However distribution may not be uniform across milk fractions. This is particularly true for mature milk, hindmilk, and postfeed milk which tend to be of higher triglyceride content, and therefore may contain higher concentrations of lipophilic AEDs[32].

NEONATAL PHARMACOKINETICS

Both gestational age and postnatal age affect the pharmacokinetics of AEDs. Hepatic and renal elimination pathways are relatively immature, making neonates prone to drug accumulation. While CYP2C9 is involved in the elimination of phenytoin (PHT), CYP2C19 metabolizes both PHT and pheobarbital (PB).Although there are subtle differences, examination of the ontogeny of these enzyme subfamilies reveals that expression is reduced or nonexistent in early fetal development and in neonates and increases during infancy (McCarver and Hines).The phase II reactions relevant to epilepsy are

catalysed by the UGTs.Lamotrigine (UGTIA4), valproate (VPA) (UGT2BI), and oxcarbazine (OXG) all are metabolized in various degrees by UGT isoenzyme enzymes. This suggest that renally eliminated AEDs [particularly LEV, gabapentine (GBP), pregabalin] may have prolonged elimination in neonates (Perucca).[36] Total and free PHT readily distribute across the placenta with a umbilical cord/ maternal concentration of 0.86-1.0 and 1.1-1.25, respectively.

HAEMORRHAGIC DISEASE IN THE NEWBORN

Enzyme inducing AEDs can produce bleeding in the newborn period.The risk of hemorrhage in neonates[35] born to women with epilepsy who were taking enzyme inducing AEDs during pregnancy is also of great concern. First described by VanCreveld and later delineated as a syndrome by Mountain et al, it has now been associated with exposure to AEDs like PB, primidone, PHT,CBZ, diazepam, amobarbital, and ethosuximide Prevalence figures are as high as 30%, but appear to average 10%.Mortality is high (over 30%) because the child is often diagnosed in a state of shock due to internal bleeding). This is due a deficiency of vitamin K-dependent clotting factors II, VII, IX, and X, in the newborn the maternal coagulation parameters being normal. A prothrombin precursor, protein induced by vitamin K absence (PIVKA), has been discovered in the serum of mothers taking AEDs. Assays (blood tests) for PIVKA may permit prenatal identification of infants at risk

for hemorrhage Prevention of neonate bleeding has only been evaluated in studies where the newborns all received intramuscular vitamin K injections 1mg at birth.[40] Whether AEDs would be associated with increased rates of hemorrhage in the newborn if this dose of vitamin K were not given remains unclear. Nonetheless, vitamin K supplementation 10-20mg/day of oral vitamin K during the last 2-4 weeks of pregnancy or 10mg intravenously during labour) is suggested, but again , to prevent bleeding in newborn, but this has been disproved in the latest study.[43]

MANAGEMENT OF EPILEPSY AND PREGNANCY

Women with epilepsy who take antiseizure medicines have successful and unremarkable pregnancies the majority of the time.[43] Achieving adequate seizure freedom is important for successful present and future pregnancies, as it is highly predictive of seizure freedom during pregnancy. From data obtained from the general population, vitamin supplementation in the form of preconceptal folic acid intake is important to prevent birth defects, and in epileptic women of child-bearing age should be encouraged to take folic acid supplements daily. Vitamins supplementation is routinely used by women planning pregnancy to ensure an adequate nutritional status. The inclusion of vitamin supplementation is important for the prevention of fetal abnormality. An early landmark large randomized, controlled trial evaluating vitamin dietary supplementation beginning at least 28 days before conception until at

least two menses were missed showed fewer malformations in the vitamin supplemented group .

In addition, it was shown that there were no neural tube defects in the vitamin supplemented group (Czeizel and Dudas)[40] Folic acid supplementation appears to be of particular importance in the prevention of neural tube defects.[41] It has been suggested that the incidence of major congenital malformations may be increased where supplemental folic acid is lacking (Vajda et al). (13,42)

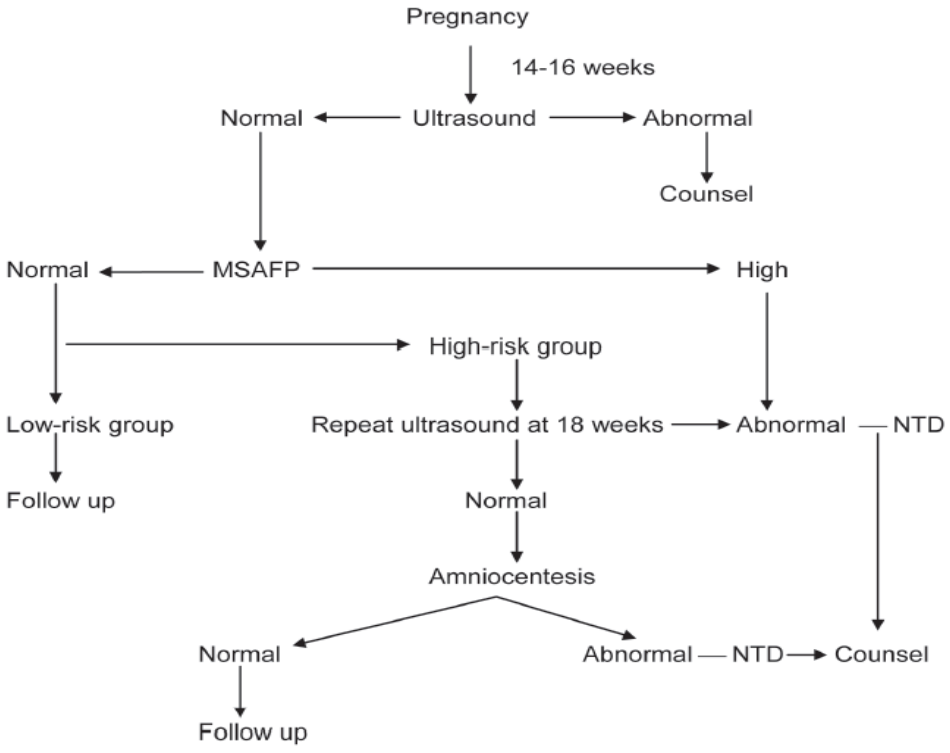
All pregnant women should be offered screening for aneuploidy and/or invasive diagnosis for chromosomal abnormalities (first trimester chorinic villous sampling or second trimester genetic amniocentesis) in those at high risk. There are several screening tests available for trisomy 13,18,and 21. The most common of which is trisomy21 which is known as Down's syndrome. All of these aneuploidies increase in incidence as the women's age increases.The number of screening test available also has recently increased. There is now a wide range of screening tests that combine first trimester ultrasound (measurement of the fetal nuchal translucency, a sonolucent area at the back of the fetus's neck, and the presence or absence of the fetal nasal bone) with first and second trimester maternal serum analysis. These include first trimester placental associated pregnancy protein A [PAPP-A] and beta

human chroinic gonadotrophin [hCG] and second trimester alpha fetoprotein [MSAFP], inhibin,beta human chrionic gonadotrophin [BhCG], and estriol.

POSITIVE FAMILY HISTORY FOR MALFORMATION AND AEDS

Birth defects associated with use of medications often result from a "multi-factorial inheritance" that is a combination of genetic make-up and environmental exposure. In these cases, the individual may inherit one or more genes that may increase the predisposition to birth defects if there is exposure to certain environmental substances (such as AEDs).These individuals have the genetic predisposition to a birth defect but may not develop it unless there is exposure to particular substance during its early development

PROTOCOL FOR SCREENING OF CONGENITAL MALFORMATIONS (Sanjeev Thomas etal) [27,29]



PRENATAL CARE:

During pregnancy, patients with seizure disorder for the most part should be cared for like any other pregnant woman. The main differences are that women with epilepsy are followed for their seizure activity and they may be screened more intensively for fetal anomalies and cautioned about regular AED intake.

PREGNANCY REGISTRIES:

The first pregnancy registry to monitor the safety of an AED was the International Lamotrigine Pregnancy Registry,established by Burroughs Welcome (now GlaxcoSmithKline) in 1992 (Cunnington and Tennis).

Subsequent AED pregnancy registries have been established by independent academics groups or physician networks with the exception of the gfcsingle drug Keppra Pregnancy Registry established in 2004 by UCB Pharma (Magnus).The first multidrug AED pregnancy registry was initiated in the UK in 1996 with educational grants from the Epilepsy Research Foundation and various pharma companies. In addition to voluntary reports from healthcare providers,women can directly enroll themselves in the UK Epilepsy and Pregnancy Registry by telephoning a toll free number, though all exposure and follow-up information is sought through the healthcare provider (Russell et al.,). The multipharma company-sponsored North American Antiepileptic Drug (NAAED) registry (also known as AED Pregnancy

Registry), also established in 1996, followed collecting data across the United States and Canada. This was the registry to rely solely on women directly enrolling themselves with telephone interviews at enrolment, during pregnancy and after delivery. Informed consent is additionally sought for medical record review of outcomes (Holmes et al)[45]

The European Registry for Antiepliptic Drugs (EURAP)[14] was the last multi AED registry to be informed in 2000 and grown to collect data in more than 40 countries across Europe, Asia, and South America(Tomson et al.,[14].Although an international registry offers many advantages, including increased recruitment and greater generalizability, there are also significant challenges in working across different healthcare settings. EURAP has met these logistic challenges by working in a standardized protocol and ensuring a consistent case definition with all defects reviewed by two protocol and ensuring a consistent case definition with all defects reviewed by two physicians at the central coordinating center.[14] The single country AED pregnancy registries in the UK and Australia also report into EURAP.

In India the pregnancy registry is set up at kerala by Sanjeev Thomas.

Current regulatory guidance on establishing pregnancy registries offers many methodological options while maintaining scientific rigor.

The key value of the pregnancy registry design is enrollment of women exposed to the AED prior to conception and before the pregnancy outcome is known. This increases the accuracy of the exposure reporting and reduces the bias associated with retrospective reporting which can over represent more severe and unusual cases. However, the prevalence and timing of antenatal testing has made it increasingly difficult to recruit women into the registries before they have any knowledge of fetal health.

AIM OF THE STUDY

1. To study the alteration of seizure frequency during pregnancy.
2. To study the outcome of pregnancy in women with epilepsy.
3. To study the outcome of delivery in epileptic pregnant women.
4. To study the effect of epilepsy, and antiepileptic drugs on the foetus and neonate.
5. To compare the outcomes of pregnancy in patients with or without preconceptal counseling.

MATERIALS AND METHODS

Material/selection of subjects: WWE in the reproductive age group who were planning pregnancy or became pregnant were included in the study. Patients with epilepsy attending epilepsy clinic at Institute of Neurology Chennai and also RIOGH Egmore who were on antiepileptic drugs before and during pregnancy were enrolled. All patients followed up through out the course of pregnancy, and 3 months postpartum.

Exclusion criteria:

Patients with first episode of seizure during pregnancy, seizure due to complications of diabetes or hypertension, or taking antiepileptic drugs after the first trimester were excluded.

Methods/Analysis:

Demographic profile of patients obtained. Detailed history obtained regarding the age of onset of epilepsy, duration, seizure type, frequency of seizures dosage of AEDs, no of drugs. Detailed neurological examination was done EEG, and MRI Brain done in all patients. Women and their families are educated about the potential risks before they become pregnant. Risk factors for adverse pregnancy outcomes like nutritional status (obese and underweight women, or other intercurrent illnesses (diabetes, hypertension, urinary tract

infection.) are assessed. To start risk reduction prior to conception in all WWE.

The following maternal characteristics were analysed.

Seizure type during pregnancy is classified according to International league against epilepsy . Whether there is increase in seizure frequency during pregnancy.. Number of antiepileptic drugs and their individual minimum and maximum dosages were noted.

Whether the patient is on monotherapy or polytherapy. In polytherapy various drug complications are analyzed like (phenytoin+ carbamazepine, phenytoin + carbamazepine+ sodium valproate, sodium valproate+ carbamazepine, sodium valproate+ phenytoin, sodium valproate+ phenytoin+ levetiracetam.

Correlation of drug dosage with foetal outcome.

The dosage of individual drugs required is analysed.Patient kept on the lowest and effective dosage required to control seizures.

All patients are encouraged to take folic acid 5mg prior to conception regularly. Women with epilepsy who were in the reproductive age group are counseled to take folic acid in the preconceptual period regularly.

Obstetric data obtained from their antenatal records.,which included gestational age at booking ,preconceptal folic acid intake, Hyperemesis gravidarum, pre-eclampsia. Abruptio placentae, premature labor has been watched for carefully in these women, for they predispose to poor drug intake and seizures.

Screening for foetal characters in the first, second and third trimester. To watch for neural tube defects in the first trimester. Alpha foetal protein assay was done as and when required. In the second trimester targeted anomaly scan was done and looked for major defects which include cardiac defects, and urogenital defects. In the third trimester, to look for IUGR, birth hypoxia, oligohydramnios, and other congenital anomalies, to asses the adequacy of liquor, congenital anomalies, birth weight.

Mode of delivery:

Pregnancy outcome assessed spontaneous loss before 20 weeks of gestation foetal still births after 20weeks, live births. Premature delivery was defined as delivery before gestational week 37, and prolonged pregnancy as lasting longer than 42 weeks

Whether the patient underwent induced or spontaneous labour, instrumentation during labour, elective or emergency caesarian section. Types of anaesthesia and their mode of administration looked for.

Seizure outcome in the postnatal period:

Patients in the postnatal period are monitored for the increased seizure frequency because of the increased stress of the postnatal period and sleep deprivation and motivated for regular drug intake.

FOETAL OUTCOME :

Apgar score at 1minute,5minutes, birth weight,head circumference , major and minor congenital anomalies , specific drug related abnormalities are assesed. Vitamin K is given for all babies after delivery. Small-for-gestational-age newborns are defined when they are below the tenth percentile when adjusted to the gestational age and sex for the normal population. Infants with birth weight <2,500 g were considered to have low birth weight. Major malformations were defined as structural abnormalities with surgical,medical, or cosmetic importance and were identified by the pediatrician, who examined the infants at birth and at discharge from the hospital.

To provide adequate breast feeding and neonatal care and to monitor for feeding difficulties.

RESULTS

DEMOGRAPHIC PROFILE :

The mean age of the patient was 25.09,maximum age was 39.75% of them had prenatal counseling before their pregnancy

Table – 1 MATERNAL AGE

		AGE	GES AGE
N	Valid	100	100
	Missing	0	0
Mean		25.02	13.33
Median		25.00	12.00
Std. Deviation		4.339	3.279
Minimum		16	8
Maximum		39	24

TABLE – 2 PARITY

Among 100 pts examined 52% were primigravida,48% multigravida..

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Primi	52	52.0	52.0	52.0
	Multi	48	48.0	48.0	100.0
	Total	100	100.0	100.0	

TABLE - 3 EDUCATIONAL STATUS

On viewing their educational status, 30 % of them were found to be illiterate,54 % attained primary education, 11% secondary education ,only 5 % reached upto college.

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Illiterate	30	30.0	30.0	30.0
	Primary	54	54.0	54.0	84.0
	secondary	11	11.0	11.0	95.0
	Above secondary	5	5.0	5.0	100.0
	Total	100	100.0	100.0	

TABLE - 4 WORKING STATUS

Most of them were home makers constituting about 92% ,8% of them were working women.

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	House wife	92	92.0	92.0	92.0
	Working	8	8.0	8.0	100.0
	Total	100	100.0	100.0	

TABLE -5 CAUSES FOR SEIZURES

Among 100 patients about 47 of them had either CVT, active granuloma,calcified lesions, benign tumors, and 53 of them were idiopathic.99 had a normal neurological examination,one had a left hemiparesis with

hemiatrophy.53 had a normal imaging either by CT or MRI and 47 had some abnormality on neuroimaging.The EEG was normal in 42,abnormal in 58.

ETIOLOGY	IDIOPATHIC 53	ACQUIRED 47
NEUROLOGICAL EXAMINATION	NORMAL99	LEFT - 1HEMIPARESSIS
IMAGING	NORMAL 53	ABNORMAL 47
EEG	NORMAL 42	ABNORMAL58

TABLE – 6 PRECONCEPTUAL FOLIC ACID INTAKE

Folic acid was taken by most of them preconceptal amounting to 96 %. 4% of them never consumed folic acid prior to pregnancy.

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Taken	96	96.0	96.0	96.0
	Nottaken	4	4.0	4.0	100.0
	Total	100	100.0	100.0	

TABLE -7 COMPLICATIONS

One women developed GDM during her pregnancy course,2 of them developed pregnancy induced hypertension. 70% of the pregnant women with epilepsy were suffering from anemia. (hyperemesis gravidarum) occured more frequently in these women , which made them difficult to take oral medications.

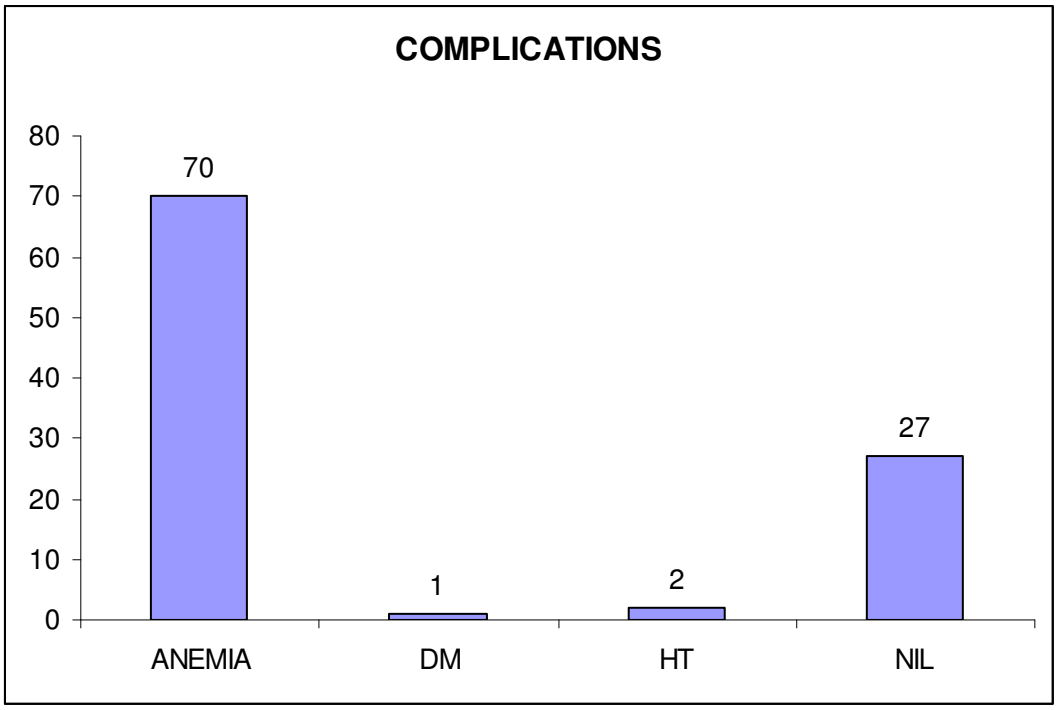


TABLE – 8 MATERNAL SEIZURE PROFILE AND ANTIEPILEPTIC DRUG INTAKE

On viewing their epileptic diary it was found that 81% had generalised tonic clonic seizures,12 % complex partial seizures,2 % simple partial seizures with secondary generalisation,5 % complex partial seizures with secondary generalisation

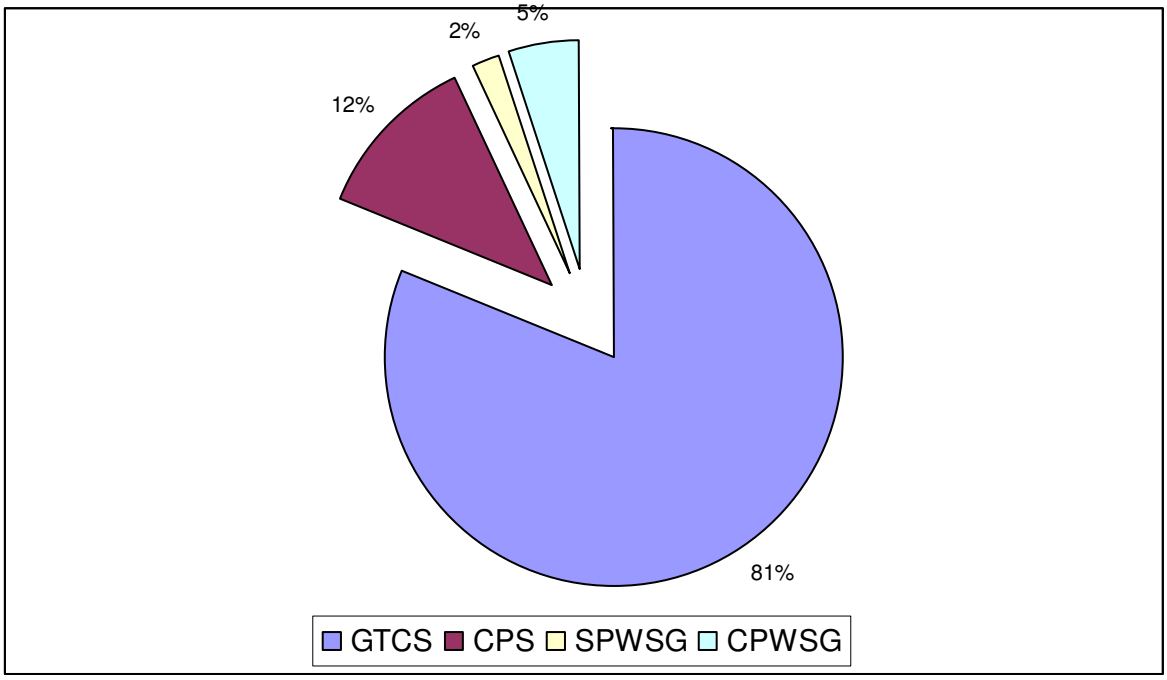


TABLE -9 ANTEPARTUM SEIZURE FREQUENCY

83 of 100 patients had good seizure control prior to pregnancy .10 of these 83 had increased seizures during pregnancy . 17 of those 100 who had poor seizure control prior to pregnancy also noted an increase in seizure frequency during pregnancy .1% developed status epilepticus. Age of onset of epilepsy , duration , and etiology had no relationship to seizure occurrence.

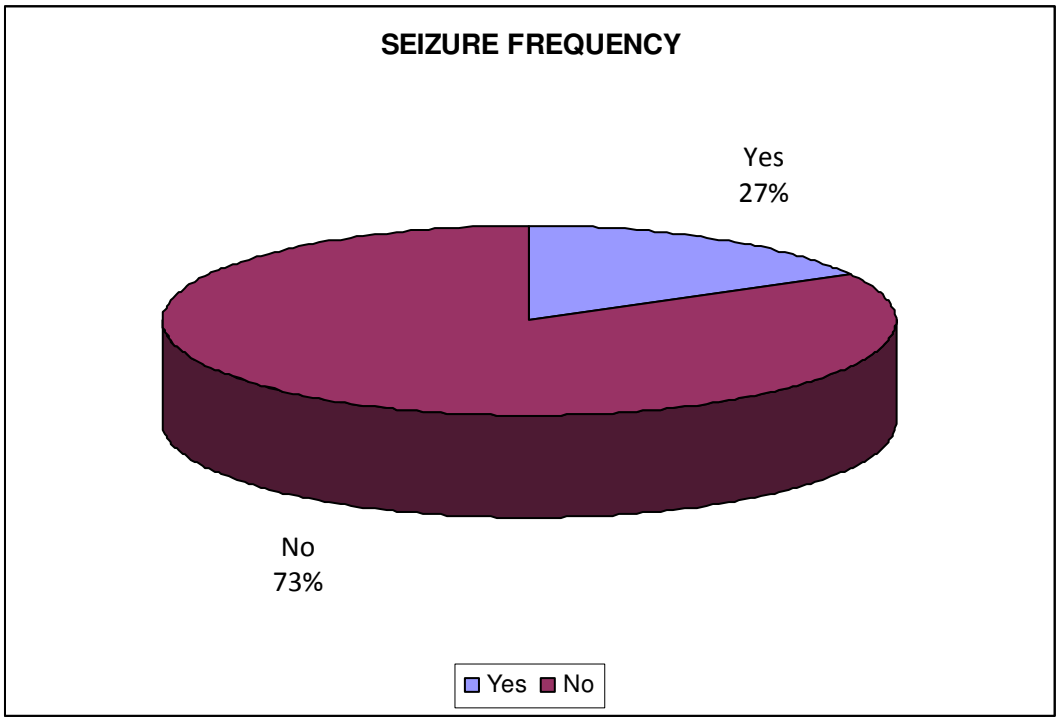


TABLE -10 AED MONOTHERAPY

Out of 100 , 72 of them on monotherapy with either phenytoin 42, carbamazepine 23, and sodium valproate 7.

DRUGS	FREQUENCY	PERCENT
PHENYTOIN	42	58.33
CARBAMAZEPINE	23	31.94
SODIUM VALPROATE	7	9.72
TOTAL	72	100.0

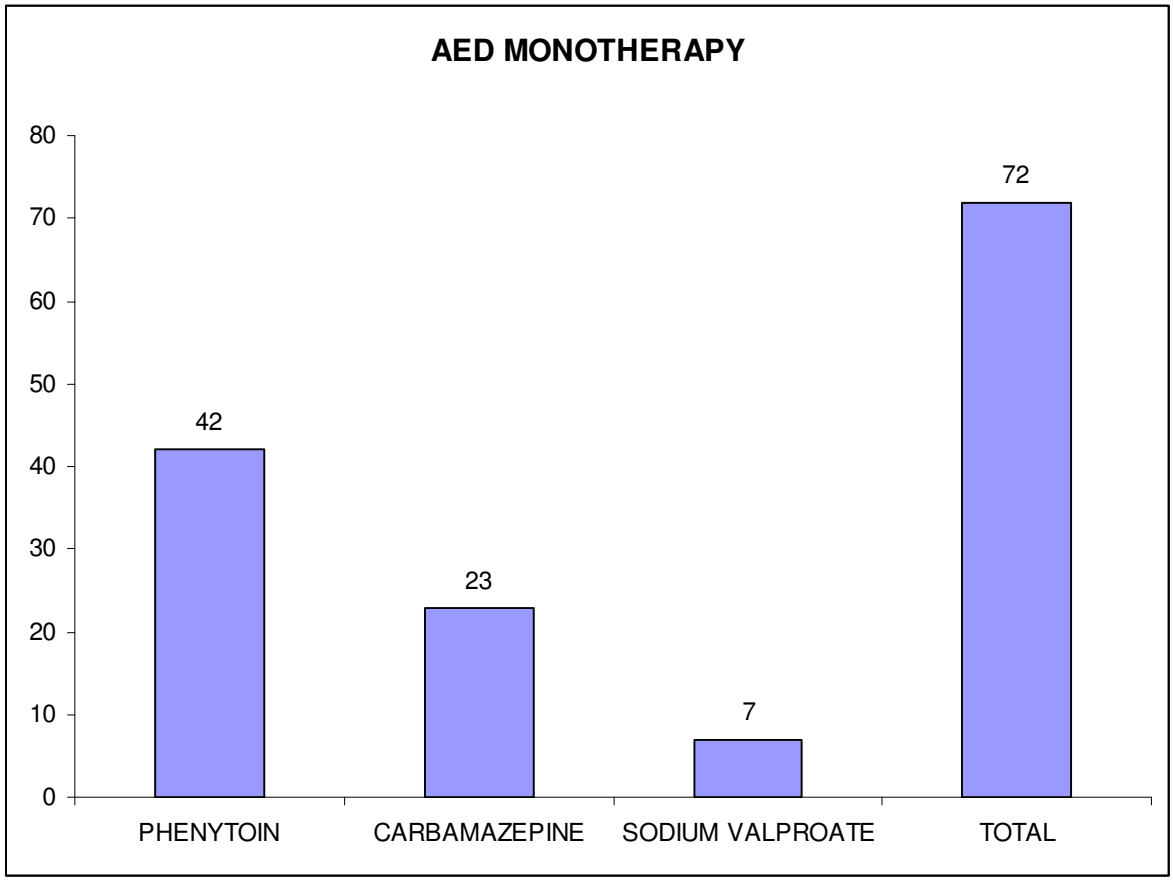


TABLE -11 AED INTAKE ON TWO DRUG REGIMEN

Out of 100 , 20 on two drug combinations with CBZ+SVP -5, CBZ+PHT-1, SVP +CBZ-3,PHT+SVP-7,PHT+CBZ-4.

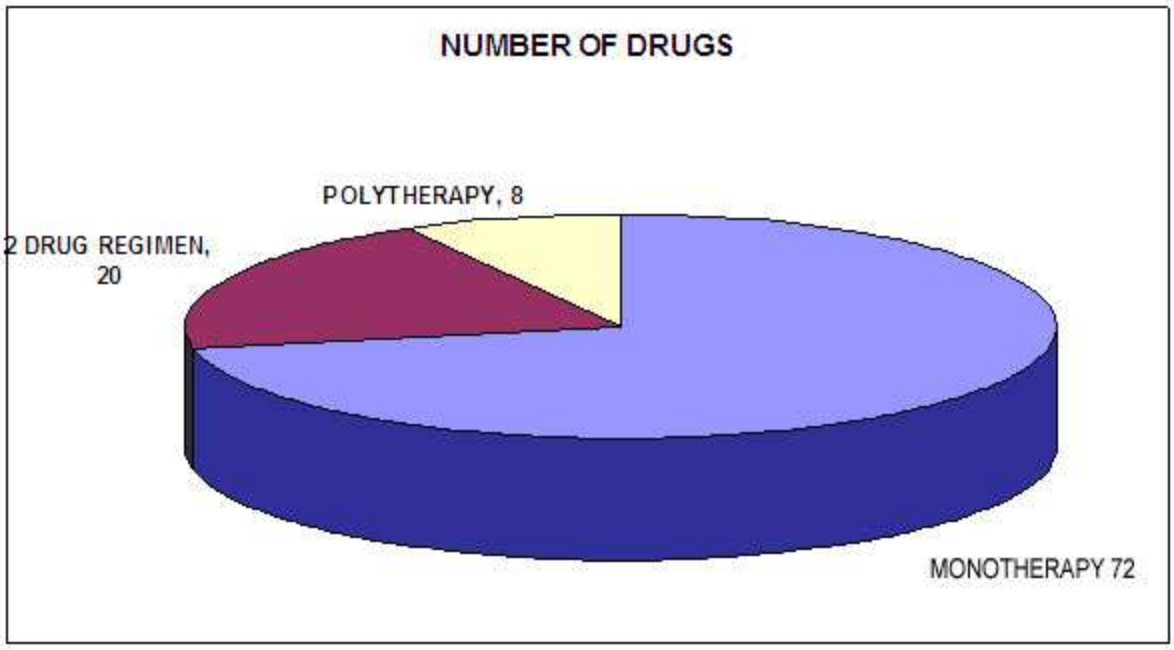
DRUG COMBINATION	FREQUENCY	PERCENT
CBZ+SVP	5	25.0
CBZ +PHT	1	5.0
SVP+CBZ	3	15.0
PHT+SVP	7	35.0
PHT+CBZ	4	20.0
TOTAL	20	100.0

TABLE - 12 : AED INTAKE 3 DRUG REGIMEN

DRUG COMBINATION	FREQUENCY	PERCENT
CBZ+SVP+PHT	2	25.0
CBZ+PHT+PHB	1	12.5
CBZ+PHT+SVP	1	12.5
PHT+SVP+LEV	2	25.0
CBZ+SVP+LEV	2	25.0
TOTAL	8	100.0

TABLE- 13 :NO OF DRUGS

Out of 100 patients 72% on monotherapy, 20% on two drug regimen,8% on polytherapy.



The dose of aeds ranged from 200mg -400mg for phenytoin, 400mg -600mg for sodium valproate), 400mg -1200mg for carbamazepine) 4 of them on 100mg of phenytoin,

Table – 14 : CHANGE OF_DRUG

About 21% had a change in the drug dosage during their pregnancy and 79% maintained their prepregnancy drug dosage .

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Yes	21	21.0	21.0	21.0
	No	79	79.0	79.0	100.0
	Total	100	100.0	100.0	

Ultrasound evaluation done under high resolution during the first trimester did not reveal any abnormality in any of them.2 had neural tube defects during the third trimester.5 of them were diagnosed with congenital malformations after delivery.

PREGNANCY OUTCOME

DURATION OF DELIVERY

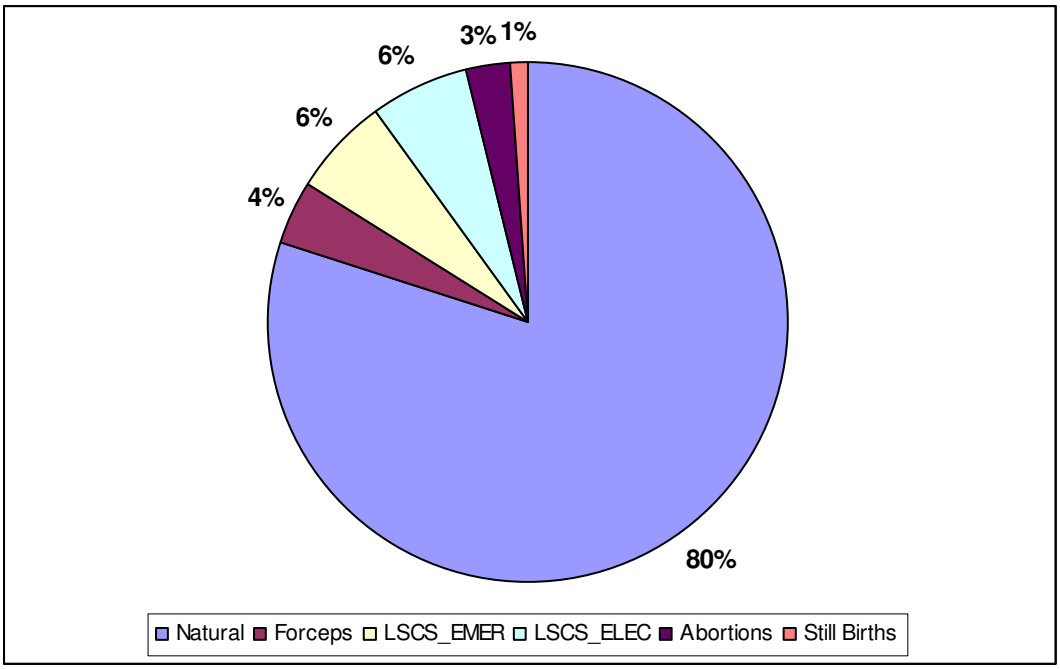
87% had an uveventful course throughout their pregnancy and delivered at term.9% had preterm delivery.80% had normal vaginal delivery at term.4% had difficult labour and delivered by forceps, 3 had abortion, one of them had still birth ,and all of them had good seizure control during pregnancy 6% emergency LSCS,6% had elective LSCS. because of foetal distress. 12% underwent LSCS for obstetrical indication.The indication for emergency LSCS was difficult labour with failed induction, foetal distress, a big baby.

Table – 15

	Frequency	Percent	Valid Percent	Cumulative Percent
Term	87	91.0	91.0	91.0
Preterm	9	9.0	9.0	100.0
Total	96	100.0	100.0	

MODE OF DELIVERY

	Frequency	Percent
Natural	80	80.0
Forceps	4	4.0
LSCS_EMER	6	6.0
LSCS_ELEC	6	6.0
Abortions	3	3.0
Still Births	1	1.0
Total	100	100.0



4% developed postpartum haemorrhage none of them had antepatum haemorrhage. 4% developed postpartum seizures.

POST PARTUM

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Seizure	4	4.0	4.0	4.0
	No seizure	96	96.0	96.0	100.0
	Total	100	100.0	100.0	

FOETAL OUTCOME

5 had apgar score of less than 5 at 1 minute.which improved to 7 or more at 5 minutes.

APGAR_1M

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	2	3	3.0	3.0	3.0
	3	2	2.0	2.0	5.0
	5	31	31.0	31.0	36.0
	6	39	39.0	39.0	75.0
	7	24	24.0	24.0	99.0
	8	1	1.0	1.0	100.0
	Total	100	100.0	100.0	

APGAR_5M

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	7	49	49.0	49.0	49.0
	8	45	45.0	45.0	94.0
	9	6	6.0	6.0	100.0
	Total	100	100.0	100.0	

25% had low birth weight of below 2.5kg, 75% had a normal birth weight between 2.5 kg to 3.5kg.

BWT

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	LBW	25	25.0	25.0	25.0
	NOT_LBW	75	75.0	75.0	100.0
	Total	100	100.0	100.0	

.AED DRUG THERAPY AND CM

NO_DRUGS	1	Count	4	68	72
		% within NO_DRUGS	5.6%	94.4%	100.0%
	2	Count	2	18	20
		% within NO_DRUGS	10.0%	90.0%	100.0%
	3	Count	1	7	8
		% within NO_DRUGS	12.5%	87.5%	100.0%
Total		Count	7	93	100
		% within NO_DRUGS	7.0%	93.0%	100.0%

Chi-Square Tests

	Value	df	P-value)
Pearson Chi-Square	.879[a]	2	.644
Likelihood Ratio	.800	2	.670
Linear-by-Linear Association	.853	1	.356
N of Valid Cases	100		

a. 2 cells (33.3%) have expected count less than 5. The minimum expected count is .56.

PREGNANCY COMPLICATIONS AND CM

			cong_malf		
			Yes	No	Total
COMPLI	Nil	Count	7	89	96
		% within COMPLI	7.3%	92.7%	100.0%
	DM	Count	0	1	1
		% within COMPLI	.0%	100.0%	100.0%
	HT	Count	0	2	2
		% within COMPLI	.0%	100.0%	100.0%
	Hydromins	Count	0	1	1
		% within COMPLI	.0%	100.0%	100.0%
Total		Count	7	93	100
		% within COMPLI	7.0%	93.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	.314[a]	3	.957
Likelihood Ratio	.593	3	.898
Linear-by-Linear Association	.275	1	.600
N of Valid Cases	100		

a. 6 cells (75.0%) have expected count less than 5. The minimum expected count is .07.

SEIZURE TYPE AND CM

			cong. malf		
			Yes	No	Total
TYPE EPI	GTCS	Count	4	77	81
		% within TYPE EPI	4.9%	95.1%	100.0%
	CPS	Count	1	11	12
		% within TYPE EPI	8.3%	91.7%	100.0%
	SPWSG	Count	1	1	2
		% within TYPE EPI	50.0%	50.0%	100.0%
	CPWSG	Count	1	4	5
		% within TYPE EPI	20.0%	80.0%	100.0%
Total		Count	7	93	100
		% within TYPE EPI	7.0%	93.0%	100.0%

Chi-Square Tests

	Value	df	P value
Pearson Chi-Square	7.540[a]	3	.057
Likelihood Ratio	4.203	3	.240
Linear-by-Linear Association	3.802	1	.051
N of Valid Cases	100		

a. 5 cells (62.5%) have expected count less than 5. The minimum expected count is .14.

MODE OF DELIVERY IN PATIENTS WITH CM

			cong_malf		
			Yes	No	Total
mod_type	Natural	Count	7	77	84
		% within mod_type	8.3%	91.7%	100.0%
	Forceps	Count	0	4	4
		% within mod_type	.0%	100.0%	100.0%
	LSCS_EMER	Count	0	6	6
		% within mod_type	.0%	100.0%	100.0%
	LSCS_ELEC	Count	0	6	6
		% within mod_type	.0%	100.0%	100.0%
Total		Count	7	93	100
		% within mod_type	7.0%	93.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	1.434[a]	3	.698
Likelihood Ratio	2.539	3	.468
Linear-by-Linear Association	1.223	1	.269
N of Valid Cases	100		

a. 4 cells (50.0%) have expected count less than 5. The minimum expected count is .28.

CONGENITAL MALFORMATIONS TABLE 21

COMPLICATIONS	AGE	PARITY	FOLIC ACID	GESTATIONAL AGE	SEIZURE TYPE	AED INTAKE	AED DOSAGE	DELIVERY	MODE OF DELIVERY	POSTPARTUM	APGAR 1MT	APGAR 5MT	BIRTH WEIGHT
DERMOID CYST	22	PRIMI	YES	12	GTCS	PHT	300 MG	TERM	NATURAL	NO	5	8	2.75
VSD	24	PRIMI	YES	14	GTCS	CBZ	1000 MG	TERM	NATURAL	NO	7	9	3
ASD	23	PRIMI	YES	13	GTCS	PHT	300 MG	TERM	NATURAL	NO	6	8	3
ARNOLD CHIARI	26	PRIMI	YES	12	CPSWS	PHT	300 MG	PRETERM	NATURAL	NO	5	7	2.5
MENINGOCELE	25	MULTI	YES	12	GTCS	PHT/SVA	200/600	TERM	NATURAL	NO	6	7	2.75
MYELOMENINGOCELE	26	PRIMI	YES	20	SPWSG	SVA /CBZ	200	TERM	NATURAL	NO	6	9	2.5
SPINA BIFIDA	33	PRIMI	YES	14	CPS	PHT/CBZ / VPA	200/400/400	TERM	NATURAL	NO	5	7	2.6

Malformations occurred in 6% of primigravida, and 1% of multigravida. 72 % out of 100 patients were on monotherapy with 42 % on phenytoin ,23% on carbamazepine and 7% on sodium valproate.The incidence of congenital malformations was 3 in those on phenytoin, 1 in carbamazepine.

20 of 100 patients were on two drug regimen In SVP+CBZ combination CM occured in 1, with PHT+SVP is 1. Among 8 of them on polytherapy one had malformation . The relation between drug regimen and congenital malformations is 5.6%(4 of 72) on monotherapy, 10.0%(2 of 20) on two drug regimen,12.5% (1 of 8) on polytherapy. Among those who presented with malformations 4 had generalised tonic clonic seizures,one with Complex partial seizures, one simple partial with secondary generalisation, one had complex partial seizures with secondary generalisation. All of them had preconceptal intake of folic acid and had no contributory risk factors like gestational diabetes , preeclampsia, or eclampsia.

Children with CM were delivered per vaginum naturally. 6 of the neonates with congenital malformations delivered at term ,1 at preterm. The major congenital malformations observed are 1 had dermoid cyst, 3 had neural tube defects, Arnoldchiari mal formation, meningocele, meningomyelocele, spinabifida. 2 with cardiac disorders Ventricular septal defect, atrial septal defect detected 1 month after delivery.

All the neonates had a good apgar score at 1 and 5 minutes despite their malformations.But feeding difficulties were encountered in 2 neonates with cardiac malformations.1 baby had an N ICU admission.

DISCUSSION

Women with epilepsy usually fear the risk of pregnancy complications and birth defects would be higher because of seizures and because her baby will be exposed to antiepileptic drugs. However, many women with epilepsy and their treating physicians believe these risks to be higher than they really seemed to be.

Our study was mainly done in WWE who took AEDs prior to and during pregnancy.Consanguinous parentage was excluded from our study to minimise the role of genetic factors on the foetal outcome.

According to Richmond et al [28] there was a increased risk of PIH [< 0.5] in WWE. The rate of preeclampsia was not significantly increased in a prospective study of 179 pregnancies of WWE in singleton pregnancy at finland.[46] In A Swedish study by Christina philo etal done on 1207[29] women taking AEDs in pregnancy found a significant increase in the incidence of pre-eclampsia (OR 1.66, 95% - CI 1.43–1.89). There was no increased risk of preeclampsia or GDM in our study population.

The EURAP registry[14] on 1882 WWE recorded seizure freedom in 58% of participants during pregnancy. When first trimester seizure activity

was used a reference, 64% had no change in the second and third trimester, 16% improved, while only 17% deteriorated. The Australian Register by (Vajda et al)[47] found that an year of seizure freedom prior to conception reduced the pregnancy risks of having seizures by 50-70%. But in our study 27 % had an increase in their seizure frequency in the antepartum period . In 17 of them it was either because of poor drug compliance, fear of intake of antiepileptic drugs causing congenital malformations in the child and one among them developed status epilepticus , not able to procure drugs because of their shift of residence, but some of them developed seizures despite good drug compliance.73% had no increase in seizure frequency. There was no relationship between the seizure duration and frequency of seizures.The increase in frequency occurred both in generalized and partial epilepsy groups.

Walker et al [48] reported that Women with good seizure control (e.g. seizure free for 2–5 years) may be eligible to stop or reduce their medication prior to pregnancy, and women taking more than one AED may be considered a trial of monotherapy, if they have normal neurological examination/IQ, EEG and neuroimaging, for the risk of getting a seizure is much lower. In our study 27% had a change in medication to monotherapy because of good seizure control.All of them had a normal neurological examination and EEG.

Epileptic pregnant women have a higher induction rate . This has been reported with two previous studies in which 33% and 19% were induced, but contrary to the finding in a study from Japan [49] where no difference was seen. According to guidelines in Norway and England [50], epilepsy is not an indication for induction in uncomplicated pregnancies. The induction rate was low in our women 4 of them were induced and delivered by forceps, and most of them had spontaneous vaginal delivery.12% of 100 patients, delivered by caesarian section, 6 by elective, 6 by emergency LSCS due obstetrical causes.

An increase in vaginal bleeding during late pregnancy and delivery, has been reported with previous studies (Pennell; Pilo et al.)[51, 29] but in our study group 4 patients developed PPH. Alterations in vitamin K metabolism may also be a causal factor (Crawford; Pilo et al.) [52,29] possibly associated with use of enzyme-inducing AEDs.

EURAP registry[14] data regarding the impact of seizures on pregnancy outcome in 1956 WWE, had a stillbirth rate of (1.5%) which is higher than that in the general population of 0.5% Earlier reports have suggested higher mortality in infants born to mothers with epilepsy; Hiilesmaa et al.; Meador et al[35,37,31) due to poor control of maternal seizure LaJoie & Moshe[10,35]. There was 1 abortion, 3 still births in our study. No neonatal deaths were seen.

FOETAL OUTCOME

Low birth weight and low apgar score was seen in epileptic mothers exposed to AEDs in the literature.[57,58]. In our study low birth was seen in 25% of the mothers exposed to AEDs. 5 of 100 neonates had an apgar score of less than 5 at 1minute which improved to 7 or more at 5 minutes, leading to favourable birth outcomes in our study group.

The U.K. registry(39) reported a higher malformation rate with VPA, 5.9% (4.3–8.2%; 95% CI), than with CBZ (2.3% [1.4–3.7%]) or LTG (2.1% [1.0–4.0%]).The types of congenital malformations found in pregnancies exposed to monotherapy with either carbamazepine, valproate, and phenytoin were similar to those previously reported abnormalities. An American Academy of Neurology Practice Parameter (25) concluded the increased the risk for major congenital malformations associated with AED intake during the first trimester and with polytherapy.

The incidence of malformations for monotherapy was for carbamazepine 4.6% , lamotrigine 2.9%, phenobarbitol 4.9% , phenytoin 7.4% and valproate 10.7% , with VPA having a higher dosage related relation either as monotherapy or polytherapy. .[13,42,53]. The rate of congenital malformations is 2 to 3% in the general population, reported rates in offspring of women with

epilepsy ranged from 1.25 to 11.5%, with the combined estimates yielding a rate of 4 to 6%. Previous studies by reports [39,42,51,53) reported an increase in congenital malformations. In our study 7 of 100 WWE delivered a child with congenital malformations. In monotherapy group it was 7.142% (3 of 42) on therapy with phenytoin,4.34% (1 of 23) on carbamazepine. On 2 drug regimen it was 1 with SVP+PHT,1 with CBZ+SVP. In polytherapy group it was 12.5%(1 of 8). CM risk is 5.6% on monotherapy ,10.0% on two drug regimen,12.5% on polytherapy.

The congenital malformations in our group are Neural tube defects, cardiac malformations, dermoid cyst. The relative risk of malformations was higher with monotherapy and polytherapy in our epileptic pregnant women. Studies have shown that folic acid is effective in reducing malformations in the general population, but not in AED-exposed pregnancies. Studies have revealed an association between CBZ exposure in utero and NTDs. (54, 55, 56) NTDs occur in 6/10,000 pregnancies. Lingh et al has associated spinabifida aperta as the specific NTD associated with VPA & CBZ exposure. (55)

Neural tube defects, can be prevented if folic acid is initiated pre-conceptually [40,41], and every effort must be taken to improve folic acid supplementation in women with epilepsy , and majority of our patients were on preconceptual folic acid including those with congenital malformation .In

our study, preconceptal folic acid supplementation was higher in AED-treated pregnancies, especially when treated with valproate or polytherapy.

A prospective multicenter, observational study revealed that fetal exposure to valproate resulted in significantly lower IQ at age 3 compared to carbamazepine, lamotrigine, or phenytoin. The effect of valproate on lowering fetal IQ was dose dependent. In our study the dose of valproate was significantly reduced without affecting the seizure frequency.[31]

CONCLUSION

1. Most of our pregnant patients had good seizure control before and during pregnancy.
2. In those with poor seizure control prior to pregnancy had improved seizures during pregnancy, due to stringent monitoring and care.
3. Status epilepticus occurred in one patient.
4. Most of our patients had successful vaginal delivery, in those who had caesarian section it was done for non neurological indication like cephalopelvic disproportion, foetal distress.
5. During postpartum period only four of them developed seizures .

The incidence of congenital malformations, CM risk is 5.6% on monotherapy,10.0% on two drug regimen,12.5% on polytherapy. There was no neonatal deaths.

It is important to educate pregnant women with epilepsy for proper planning of their pregnancies , for preconceptal folic acid intake, AED intake during the course of pregnancy, and also monitor with high resolution ultrasound for the detection of congenital malformations.

BIBLIOGRAPHY

1. M. Tripathi, D.C. Jain, M. Gourie Devi, S. Jain, V. Saxena, P.S. Chandra, Need for a national epilepsy control program, Annuals of Indian academy of neurology. 2012 Apr-Jun; 15(2):89-93.

2. Sridharan R, Murthy BN. Prevalence and pattern of epilepsy in India. Epilepsia 1999;40:631

3. Herzog AG. Disorders of reproduction in patients with epilepsy: primary neurological mechanisms. Seizure 2008; 17:101–10

4. Backstrom T. Epileptic seizures in women related to plasma estrogen and progesterone during the menstrual cycle. Acta Neurol Scand 1976;54:321–47

5. Abbasi, F., Krumholz, A., Kittner, S.J., and Langenberg, P. (1999). Effects of menopause on seizures in women with epilepsy. Epilepsia 40, 205-210.

6. Isojärvi JIT, Tauboll E, Herzog A. Effect of entiepileptic drugs on reproductive endocrine function in individuals with antiepileptic. CNS Drugs 2005;19:207–23

7. Annegers J, Hauser W, Elveback L, Anderson V, Kurland L. Congenital malformations and seizure disorders in the offspring of parents with epilepsy. Int J Epidemiol 1978;7:241–247

8. Thomas SV, Devi CC, Radhakrishnan K, Joshua CS. Seizure pattern during pregnancy and puerperium among women with epilepsy. Epilepsia 2000;41:198–9.

9. Adab, N., Kini, U., Vinten, J., Ayres, J., Baker, G., Clayton-Smith, J., Coyle, H., Fryer, A., Gorry, J., Gregg, J., Mawer, G., Nicolaides, P., et al. (2004). The longer term outcome of children borh to mothers with epilepsy. J. Neurol. Neurosurg. Psychiatry 75(11), 1575-1583.

10. LaJoie J, Moshe SL. Effects of seizures and their treatment on fetal brain. Epilepsia 2004;45(Suppl 8):48–52.

11. Author: Jane G Boggs, MD; Chief Editor: Selim R Benbadis, MD, Women's Health and Epilepsy. Emedicine.mescape.com. Dec 1 2011.

12. Gjerde IO, Strandjord RE, Ulstein M. (1988) The course of epilepsy during pregnancy: a study of 78 cases. Acta Neurol Scand. 78:198–205

13. Vajda FJ, Hitchcock A, Graham J, Solinas C, O'Brien TJ, Lander CM, et al. Foetal malformations and seizure control: 52 months data of the Australian Pregnancy Registry. Eur. J. Neurol 2006;13:645–654

14. The EURAP Study Group. Seizure control and treatment in pregnancy: observations from the EURAP Epilepsy Pregnancy Registry Neurology (2006); 66(3): 354-360

15. Tomson T, Battino D. Pharmacokinetics and therapeutic drug monitoring of newer antiepileptic drugs during pregnancy and the puerperium. Clin Pharmacokinet 2007;46:209–19.

16. Kilpatrick, S.J., and Matthay, M.A. (1992). Obstetric patients requiring critical care: A five year review. Chest 101, 1407-1412.

17. Pennell PB, Gidal BE, Sabers A, Gordon J, Perucca E, for the international AED pharmacology work group for the health outcomes in pregnancy and epilepsy forum. Pharmacology of antiepileptic drugs during pregnancy and lactation. Epilepsy Behav 2007; 11: 263–9.

18. Battino, D., Binelli, S., Bossi, L., Canger, R., Croci, D., Cusi, C., De Giambattista, M., and Avanzini, G. (1985). Plasma concentrations of carbamazepine and carbamazepine 10,11-epoxide during pregnancy and after delivery. Clin. Pharmacokinet. 10, 279-284.

19. Yerby, M.S., Friel, P.N., Mc Cormick, K., Koerner, M., Van Allen, M., Leavitt, A.M., Sells, C.J., and Yerby, J.A. (1990). Pharmacokinetics of anticonvulsants in pregnancy: Alterations in plasma protein binding. Epilepsy Res. 5, 223-228.

20. Tran .T.A., Leppik, I.E., Blesi, K., Sathanandan, S.T., and Remmel, R. (2002). Lamotrigine clearance during pregnancy. Neurology 59, 251-255.

21. Pennell, P.B., Newport, D.J., Stowe, S.N., Helmers, S.L., Montgomery, J. Q., and Henry, T.R. (2004). The impact of pregnancy and childbirth on the metabolism of lamotrigine, Neurology 62, 292-295.

22. Atkinson, D.E., Brice-Bennett, S., and D'Souza, S.W. (2007). Antiepileptic medication during pregnancy: Does fetal genotype affect outcome? Pediatr. Res.62, 120-127.

23. Syme, M.R., Paxton, J.W., and Keelan, J.A. (2004). Drug transfer and metabolism by human placenta. Clin. Pharmacokinet. 43, 487-514.

24. Tomson T. Gender aspects of pharmacokinetics of new and old AEDs: pregnancy and breast-feeding. Ther Drug Monit 2005;27:718-21.

25. Harden CL, Pennell PB, Koppel BS, Hovinga CA, Gidal B, Meador KJ, et al. Practice parameter update: Management issues for women with epilepsy--focus on pregnancy (an evidence-based review): Vitamin K, folic acid, blood levels, and breastfeeding: Report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment

Subcommittee of the American Academy of Neurology and American Epilepsy Society. Neurology 2009;73:142-9

26. Reghunath B. Neuroendocrine aspects of epilepsy and pregnancy in Sanjeev V. Thomas (ed) Proceedings of Workshop on fertility and pregnancy among women with epilepsy. Kerala Registry of Epilepsy and pregnancy, Trivandrum. 1998;7–11

27. Thomas SV, Sindhu K, Ajaykumar B, Devi PB, Sujamol Maternal and obstetric outcome of women with epilepsy. Seizure.2009;18(3):163-166

28. Richmond JR, Krishnamoorthy P, Andermann E, Benjamin A. Epilepsy and pregnancy: an obstetric perspective. Am. J. Obstet. Gynecol 2004;190:371–379

29. Pilo, C., Wide, K. and Winbladh, B. (2006), Pregnancy, delivery, and neonatal complications after treatment with antiepileptic drugs. Acta Obstetricia et Gynecologica Scandinavica, 85:643-646.

30. Wide K, Winbladh B, Kallen B. Major malformations in infants exposed to antiepileptic drugs in utero, with emphasis on carbamazepine and valproic acid: a nation-wide, population-based register study. Acta Paediatr 2004 Feb;93:174–176.

31. Meador K, Reynolds MW, Crean S, Fahrbach K, Probst C. Pregnancy outcomes in women with epilepsy: A systematic review and meta-analysis of published pregnancy registries and cohorts. Epilepsy Res 2008;81:1-13

32. Holmes LB, Harvey EA, Coull BA, Huntington KB, Khoshbin S, Hayes AM, et al. The teratogenicity of anticonvulsant drugs. N Engl J Med 2001;344:1132-8

33. Vajda FJ, O'Brien TJ, Hitchcock A, et al. Critical relationship between sodium valproate dose and human teratogenicity:results of the Australian register of antiepileptic drugs in pregnancy. J Clin Neurosci 2004;11:854-8.

34. Adab N, Tudur Smith C, Vinten J,Williamson PR,Winterbottom JB. Common antiepileptic drugs in pregnancy in women with epilepsy. Cochrane Database of Systematic Reviews 2004, Issue 3. Art. No.: CD004848. DOI: 10.1002/14651858.CD004848.

35. Kaaja E, Kaaja R, Matila R, Hiilesmaa V. Enzyme-inducing antiepileptic drugs in pregnancy and the risk of bleeding in the neonate. Neurology 2002;58:549–53.

36. Perucca, E., and Crema, A. (1982). Plasma protein binding of drugs in pregnancy. Clin. Pharmacokinet. 7, 336-352.

37. Meador KJ, Baker GA, Finnell RH, Kalayjian LA, Liporace JD, Loring DW, et al. In utero antiepileptic drug exposure: fetal death and malformations. Neurology 2006;67:407–412.

38. Perucca E. (2005) Birth defects after prenatal exposure to antiepileptic drugs. Lancet Neurol 4:781–786.

39. Morrow J, Russell A, Guthrie E, Parsons L, Robertson I, Waddell R, et al. Malformation risks of antiepileptic drugs in pregnancy: a prospective study from the UK Epilepsy and Pregnancy Register.J. Neurol. Neurosurg. Psychiatry 2006;77:193–198

40. Czeizel AE, Dudas I. (1992) Prevention of the first occurrence of neuraltube by periconceptional vitamin supplementation. N Engl J Med 327:1832–1835

41. Kampman M. T. Folate status in women of childbearing age with epilepsy. Epilepsy Res., 2007, 75 (1) : 52.

42. Vajda FJ, Eadie MJ. (2005) Maternal valproate dosage and foetal malformations. Acta Neurol Scand 112:137–143

43. Choulika S, Grabowski E, Holmes LB. Is antenatal vitamin K prophylaxis needed for pregnant women taking anticonvulsants? Am J Obstet Gynecol 2004;190:882–3.

44. Thomas SV. Managing epilepsy in pregnancy. Neurol India 2011;59:59-65.

45. Holmes LB, Wyszynski DF, Lieberman E. The AED (antiepileptic drug) pregnancy registry: a 6-year experience. Arch. Neurol 2004;61:673–678

46. Viinikainen K, Heinonen S, Eriksson K, Kalviainen R. Community-based, prospective, controlled study of obstetric and neonatal outcome of 179 pregnancies in women with epilepsy. Epilepsia Volume 47, Issue 1, pages 186–192, January 2006

47. Seizure control in antiepileptic drug-treated pregnancy Frank J. E. Vajda1,2, Alison Hitchcock1,Janet Graham1, Terence O'Brien3, Cecilie Lander4,Mervyn Eadi Epilepsia Volume 49, Issue 1, pages 172–176, January 2008

48. Walker S, Permezel M, Berkovic S. The management of epilepsy in pregnancy. BJOG 2009;116:758–767.

49. Nakane Y, Oltuma T, Takahashi R et al. Multi institutional study on the teratogenecity and fetal toxicity of anticonvulsants: a report of a collaborative study group in Japan. Epilepsia 1980;21:663-80

50. Delgado-Escueta AV, Janz D. (1992) Consensus guidelines: preconception counseling, management, and care of the pregnant woman with epilepsy. Neurology 42:149–160.

51. Pennell PB. (2004) Pregnancy in women who have epilepsy. Neurol Clin 22:799–820

52. Crawford P. Best practice guidelines for the management of women with epilepsy. Epilepsia 2005;46(Suppl 9):117–24.

53. Artama M, Auvinen A, Raudaskoski T, Isojarvi I, Isojarvi J. Antiepileptic drug use of women with epilepsy and congenital malformations in the offspring. Neurology 2005;64:1874–8.

54. Little BB, Santos- Ramosr, Newell JF, Maderry MC. Megadose carbamazepine during the period of neural tube closure. Obstet Gynecol 1993;83 (4 suppl 2): 705-8

55. Linghout D, Omtzigt JG,Cornel MC. Spectrum of neural tube defects in 34 infants prenatally exposed to anti epileptic drugs. Neurology 1992;42 (4 suppl 5):111-8

56. Kallen B. Maternal carbamazepine and infant spina bifida. Reprod Toxicol 1994;8:203-5

57. Veiby, G., Daltveit, A. K., Engelsen, B. A. and Gilhus, N. E. (2009), Pregnancy, delivery, and outcome for the child in maternal epilepsy. Epilepsia, 50: 2130–2139.

58. Borthen, I., Eide, M., Daltveit, A. and Gilhus, N. (2010), Delivery outcome of women with epilepsy:a population-based cohort study. BJOG: An International Journal of Obstetrics & Gynaecology, 117: 1537–1543.

PROFORMA

NAME: **AGE :** **PARITY :** **MI N NO:**

ADDRESS:

EDUCATIONAL STATUS:

- IILITERATE
- PRIMARY
- SECONDARY
- COLLEGE

WORKING STATUS:

- HOUSE WIFE
- LABOURER THROUGHOUT PREGNANCY
- LABOURER TILL IIND TRIMESTER

PRECONCEPTION- PRESCRIBED 5MG FOLIC ACID DAILY YES/NO

EPILEPTIC SEIZURE DIARY

SEIZURE FREQUENCY DURING

ANTENATAL PERIOD : INCREASED / DECREASED

POSTNATAL PERIOD : INCREASED / DECREASED

TYPE OF EPILEPSY:

- GENERALISED TONIC CLONIC SEIZURES
- SIMPLE PARTIAL SEIZURES
- COMPLEX PARTIAL SEIZURES
- SIMPLE PARTIAL WITH SECONDARY GENERALIZATION
- COMPLEX PARTIAL WITH SECONDARY GENERALIZATION

EPILEPTIC DRUG REGIME PRECONCEPTION

TYPE OF AED

- MONOTHERAPY
- PHENYTOIN
- PHENOBARBITONE
- SODIUM VALPROATE
- CARBAMAZEPINE

COMBINATION OF ANTIEPILEPTIC DRUGS

- 2 DRUGS
- 3 DRUGS
- POLYTHERAPY

LMP : EDD :

PREGNANCY BOOKING VISIT
GESTATIONAL AGE AT BOOKING

PAST HISTORY : HT/DM/RENAL DISEASE/JAUNDICE/TB/ BRONCHIAL ASTHMA

FAMILY HISTORY: HT/DM/PET/

DOSE OF AED

ANTIEPILEPTIC MEDICATION DOSE AT BOOKING:

MONOTHERAPY	COMBINATION OF ANTIEPILEPTIC DRUGS
PHENYTOIN	2 DRUGS
PHENOBARBITONE	3 DRUGS
SODIUM VALPROATE	POLYTHERAPY
CARBAMAZEPINE	

CHANGE OF MEDICATION DURING PREGNANCY : YES/NO

GENERAL EXAMINATION:

Ht Wt Thyroid PR BP

NEUROLOGICAL EXAMINATION:

INVESTIGATION : BLOOD GROUP

HIV	HbsAg	VDRL	OGTT
IMMUNISATION	CT BRAIN	MRI BRAIN	EEG

ULTRASOUND : 12-14 WKS FOR ANENCEPHALY
19-20 WKS ANOMALY SCAN
30-32WKS REVIEW

DURATION OF PREGNANCY AT DELIVERY

TERM PRETERM

MODE OF DELIVERY

NATURAL DELIVERY
ELECTIVE LSCS
EMERGENCY LSCS

COMPLICATIONS OF PREGNANCY

PIH
GESTATIONAL DIABETES MELLITUS
PLACENTA PREVIA
HYDRAMNIOS
OTHERS

INDICATION FOR CESAREAN SECTION

FOETAL DISTRESS

UTERINE INERTIA

FAILURE OF INDUCTION

CNS INDICATION

POSTPARTUM HAEMORRHAGE

FOETAL OUTCOME

TERM

PRETERM

POST TERM

MEAN HEAD CIRCUMFERENCE

MEAN BIRTH WEIGHT

APGAR SCORE 1MT/5MT

CONGENITAL MALFORMATIONS

CARDIAC
MUSCULO SKELETAL
SOFT TISSUE
SPINAL
CEREBRAL
OTHERS

CONGENITAL MALFORMATIONS DUE TO

PHENYTOIN

PHENYTOIN / PHENOBARBITONE

CARBAMAZEPINE/ SODIUM VALPROATE

CARBAMAZEPINE

POLYTHERAPY

MASTER CHART

AGE	PARITY	EDUC	W/STATUS	FOLIC	TYPE EPI	AEDS-1	AEDS-2	AEDS-3	GES AGE	SEIZURE FREQ.	DD-1	DD-2	DD-3	COMPLI	CH/DRUG	US/12-14	DELIVERYTERM	MOD	POST PARTUM	BWT	HC	APS-1 min	APS-5 min	CM
16	PRIMI	ILLETERATE	HW	YES	GTCS	CBZ			10	YES	800			N0	NO	N	TERM	Natural	O	2	N	5	7	2
18	PRIMI	ILLETERATE	HW	YES	CPWSG	CBZ	PHT		12	NO	600	200		N0	NO	N	TERM	Natural	O	2	N	6	7	2
23	PRIMI	ILLETERATE	HW	YES	GTCS	CBZ			14	YES	1200			N0	NO	N	TERM	Natural	O	2	N	5	8	2
19	PRIMI	ILLETERATE	HW	YES	GTCS	CBZ			14	YES	600			N0	NO	N	TERM	natural outlet forceps	1	2	N	7	8	2
30	PRIMI	PRIMARY	HW	YES	GTCS	CBZ	SVP	PHT	10	NO	600	200	200	N0	YES	N	TERM	N	O	1	N	7	8	2
22	MULTI	PRIMARY	HW	YES	GTCS	CBZ			12	YES	400			N0	N0	N	TERM	emergency	O	2	N	7	8	2
27	MULTI	PRIMARY	HW	YES	CPWSG	SVP	CBZ		10	NO	600			N0	NO	N	TERM	natural	O	2	N	5	7	2
26	PRIMI	PRIMARY	HW	YES	GTCS	SVP			10	NO	400			N0	NO	N	TERM	natural	O	2	N	6	7	2
21	PRIMI	PRIMARY	HW	YES	GTCS	CBZ			16	NO	600			N0	NO	N	TERM	natural	O	2	N	5	8	2
26	MULTI	PRIMARY	HW	NO	GTCS	PHT	CBZ	SVP	20	NO	200	400	600	N0	NO	N	TERM	natural	O	2	N	6	8	2
21	MULTI	PRIMARY	HW	YES	CPS	CBZ			16	NO	200			N0	YES	N	TERM	natural	O	2	N	5	7	2
34	MULTI	PRIMARY	HW	YES	GTCS	PHT			14	YES	300			N0	NO	N	PRETERM	Lscs Emergency	O	2	N	7	8	2
22	MULTI	PRIMARY	HW	NO	GTCS	CBZ			12	YES	600			N0	NO	N	TERM	natural	O	1	N	6	8	2
22	PRIMI	PRIMARY	HW	YES	GTCS	PHT	SVP		12	NO	200	400		N0	NO	N	TERM	natural	O	2	N	6	8	1
21	MULTI	PRIMARY	HW	YES	GTCS	CBZ			12	NO	1000			N0	NO	n	TERM	natural	2	2	N	5	7	2
19	PRIMI	PRIMARY	HW	YES	GTCS	PHT			14	NO	200			N0	NO	N	TERM	natural	2	2	N	5	7	2
24	MULTI	PRIMARY	HW	YES	CPS	PHT			13	NO	200			N0	NO	N	TERM	previous	O	1	N	5	7	2
23	PRIMI	SECONDARY	HW	YES	GTCS	PHT			14	NO	200			N0	NO	N	TERM	natural	O	2	N	6	7	2
19	PRIMI	SECONDARY	HW	YES	GTCS	PHT			10	NO	300			N0	YES	N	TERM	LSCS Emer	O	2	N	7	8	2
33	PRIMI	SECONDARY	HW	YES	GTCS	CBZ	PHT	PB	12	YES	400	200	30	N0	NO	N	TERM	Natural	O	2	N	6	7	1
25	PRIMI	COLLEGE	HW	YES	CPS	PHT			16	YES	200			N0	NO	N	TERM	Natural	O	2	N			2
26	PRIMI	PRIMARY	HW	YES	GTCS	SVP			12	YES	200			N0	YES	N	TERM	Natural	O	1	N	6	7	2
26	PRIMI	PRIMARY	HW	YES	GTCS	CBZ	SVP		14	NO	600	400		N0	YES	N	TERM	Natural	O	2	N	5	7	2
27	MULTI	ILLETERATE	HW	YES	GTCS	PHT			12	NO	200			HYDRAM NIOS	NO	N	TERM	Natural	O	2	N	6	8	2
23	PRIMI	ILLETERATE	WORK	YES	GTCS	CBZ			12	NO	400			N0	NO	N	TERM	Natural	O	2	N	6	8	2
25	MULTI	ILLETERATE	HW	YES	GTCS	PHT	SVP		16	NO	200	400		HT	NO	N	TERM	Natural	1	1	N	7	8	2
26	MULTI	PRIMARY	HW	YES	GTCS	PHT			12	NO	200			HT	YES	N	TERM	Natural	2	2	N	7	8	2
21	PRIMI	PRIMARY	HW	YES	GTCS	CBZ			10	YES	600			N0	YES	N	TERM	Natural	O	2	N	6	7	2
21	MULTI	PRIMARY	HW	YES	GTCS	PHT			12	NO	200			N0	NO	N	TERM	Natural	O	2	N	5	7	2
23	MULTI	PRIMARY	HW	YES	GTCS	CBZ	SVP		10	NO	600	200		N0	YES	N	TERM	Natural	O	2	N	6	8	2
21	PRIMI	SECONDARY	HW	YES	CPWSG	PHT			12	NO	200			N0	YES	N	TERM	Natural Forceps Delivery	O	2	N	3	7	2
23	PRIMI	PRIMARY	HW	YES	GTCS	PHT			14	YES	200			N0	NO	N	TERM	Natural	O	1	N	6	8	2
23	PRIMI	ILLETERATE	HW	YES	GTCS	PHT			10	YES	100			N0	NO	N	TERM	natural	O	2	N	5	7	2
22	PRIMI	ILLETERATE	HW	YES	SPWSG	SVP	CBZ		13	NO	400	400		N0	NO	N	TERM	natural	O	2	N	6	7	1
25	MULTI	COLLEGE	WORK	YES	GTCS	PHT			12	YES	200			N0	NO	N	TERM	lscs Emer	O	2	N	7	8	2
23	PRIMI	COLLEGE	HW	YES	GTCS	PHT			14	NO	200			N0	NO	N	TERM	natural	O	1	N	5	7	1
20	MULTI	SECONDARY	HW	YES	GTCS	PHT			24	NO	200			N0	NO	N	TERM	lscs emer	1	2	N	6	8	2
21	PRIMI	SECONDARY	HW	YES	CPSWG	PHT			20	NO	200			N0	NO	N	TERM	natural	2	2	N	7	8	2
26	PRIMI	PRIMARY	HW	YES	GTCS	CBZ	SVP		8	NO	1200	400		N0	YES	N	TERM	Natural	O	2	N	8	9	2
27	PRIMI	PRIMARY	HW	YES	GTCS	PHT			10	YES	200			N0	YES	N	TERM	Natural	O	1	N	6	8	2
20	PRIMI	PRIMARY	HW	YES	GTCS	PHT			12	YES	300			N0	YES	N	TERM	Natural	O	1	N	7	7	2
28	MULTI	PRIMARY	HW	YES	GTCS	PHT			14	YES	300			N0	NO	N	PRETERM	Natural	O	2	N	5	7	2
21	PRIMI	PRIMARY	HW	YES	GTCS	PHT			10	YES	200			N0	YES	N	TERM	Natural	O	2	N	5	7	2
26	MULTI	PRIMARY	HW	YES	CPS	PHT			12	YES	200			N0	YES	N	TERM	Natural	O	2	N	6	8	1
36	PRIMI	SECONDARY	HW	YES	GTCS	CBZ	SVP		14	YES	600	400		N0	NO	N	TERM	Natural	O	2	N	6	8	2
27	PRIMI	ILLETERATE	HW	YES	GTCS	CBZ	SVP	LEV	20	NO	1000	200	1000	N0	YES	N	TERM	Natural	O	1	N	6	8	2
21	PRIMI	ILLETERATE	WORK	YES	GTCS	PHT			14	NO	100			N0	NO	N	TERM	Natural	2	2	N	7	8	2
30	MULTI	ILLETERATE	WORK	YES	GTCS	CBZ	SVP	PHT	12	NO	200	400	100	GDM	NO	N	TERM	Natural	O	2	N	5	7	2
21	MULTI	ILLETERATE	HW	YES	CPS	CBZ			12	NO	400			N0	YES	N	TERM	forceps delivery	O	2	N	5	7	2

MASTER CHART

AGE	PARITY	EDUC	W/STATUS	FOLIC	TYPE EPI	AEDS-1	AEDS-2	AEDS-3	GES AGE	SEIZURE FREQ.	DD-1	DD-2	DD-3	COMPLI	CH/DRUG	US/12-14	DELIVERYTERM	MOD	POST PARTUM	BWT	HC	APS-1 min	APS-5 min	CM
31	MULTI	ILLETERATE	HW	YES	CPS	PHT			12	NO	200			N0	NO	N	TERM	natural	O	2	N	6	8	2
26	MULTI	ILLETERATE	HW	YES	GTCS	SVP			10	NO	600			N0	NO	N	TERM	natural	O	2	N	5	7	2
26	MULTI	COLLEGE	HW	YES	GTCS	CBZ	SVP	LEV	10	NO	400	200	1000	N0	YES	N	TERM	natural	O	1	N	6	9	2
21	PRIMI	SECONDARY	HW	YES	GTCS	CBZ			12	YES	200			N0	NO	N	TERM	natural	O	2	N	7	8	2
29	MULTI	SECONDARY	HW	YES	CPS	PHT			12	YES	200			N0	NO	N	TERM	natural	O	2	N	7	8	2
28	PRIMI	PRIMARY	HW	YES	GTCS	PHT	SVP		12	YES	30	400		N0	NO	N	TERM	emergencyLSCS	1	1	N	7	8	2
27	MULTI	ILLETERATE	WORK	YES	GTCS	SVP			16	YES	600			N0	NO	N	TERM	natural	O	2	N	5	7	2
18	PRIMI	ILLETERATE	HW	YES	GTCS	CBZ			12	NO	200			N0	YES	N	TERM	natural	O	2	N	5	7	2
27	MULTI	ILLETERATE	HW	YES	GTCS	PHT			14	YES	200			N0	YES	N	TERM	natural	O	2	N	7	8	2
21	PRIMI	ILLETERATE	HW	YES	CPS	CBZ			12	YES	200			N0	YES	Nomal	TERM	natural	2	1	N	5	7	2
24	PRIMI	ILLETERATE	HW	YES	GTCS	CBZ			12	NO	300			N0	NO	N	TERM	natural	O	2	N	5	7	1
26	PRIMI	ILLETERATE	HW	YES	CPWSG	PHT			12	NO	200			N0	NO	30 -32 weeks	TERM	natural	O	2	N	6	7	1
25	MULTI	SECONDARY	HW	YES	GTCS	PHT			12	NO	300			N0	NO	normal	TERM	PLSCS	O	2	N	6	7	2
21	MULTI	PRIMARY	WORK	YES	GTCS	PHT			16	NO	200			N0	NO	N	TERM	PLSCS	O	2	N	5	7	2
25	PRIMI	PRIMARY	HW	YES	CPS	CBZ			12	NO	400			N0	NO	Normal	TERM	natural	O	1	N	7	8	2
22	MULTI	PRIMARY	HW	YES	SPWSG	PHT			12	NO	200			N0	NO	Normal	TERM	natural	O	2	N	6	9	2
26	PRIMI	PRIMARY	HW	YES	GTCS	PHT	SVP		12	NO	200	400		N0	NO	Normal	TERM	natural	O	2	N	6	8	2
20	PRIMI	PRIMARY	HW	YES	GTCS	PHT	CBZ		12	NO	200	1000		N0	NO	Normal	TERM	natural	O	2	N	5	7	2
23	MULTI	PRIMARY	HW	YES	GTCS	PHT	CBZ		12	YES	200	1000		N0	NO	Normal	TERM	natural	O	1	N	5	7	2
27	MULTI	PRIMARY	HW	YES	GTCS	CBZ			10	NO	200	800		N0	NO	Normal	PRETERM	ELSCS	O	2	N	2	7	2
29	MULTI	PRIMARY	HW	YES	CPS	CBZ			10	NO	400			N0	NO	Normal	TERM	natural	O	1	N	5	7	2
30	MULTI	PRIMARY	HW	YES	GTCS	PHT	3		14	NO	200	600		N0	NO	Normal	TERM	natural	O	2	N	6	8	2
23	PRIMI	PRIMARY	HW	YES	GTCS	PHT			20	NO	200			N0	YES	Normal	TERM	natural	O	1	N	6	7	2
20	PRIMI	SECONDARY	HW	NO	GTCS	PHT	SVP		22	YES	200	400		N0	NO	Normal	PRETERM	forceps delivery	O	2	N	3	8	2
24	PRIMI	PRIMARY	WORK	YES	GTCS	PHT			12	NO	200			N0	YES	Normal	TERM	natural	O	2	N	7	9	2
35	PRIMI	PRIMARY	HW	YES	GTCS	PHT			12	NO	200			N0	NO	Normal	TERM	ELSCS	O	1	N	6	7	2
31	MULTI	PRIMARY	HW	YES	CPS	CBZ	SVP		12	NO	400	200		N0	NO	Normal	TERM	natural	O	1	N	6	7	2
19	PRIMI	PRIMARY	HW	YES	GTCS	SVP			12	NO	200			N0	NO	Normal	TERM	natural	O	2	N	7	8	2
28	MULTI	COLLEGE	HW	NO	GTCS	PHT			12	YES	200			N0	NO	Normal	TERM	natural	O	2	N	7	7	2
32	MULTI	PRIMARY	HW	YES	GTCS	PHT			20	NO	300			N0	NO	Normal	TERM	natural	O	1	N	6	7	2
39	MULTI	PRIMARY	HW	YES	GTCS	PHT	CBZ		14	NO	300	200		N0	NO	Normal	TERM	natural	O	2	N	7	8	2
23	MULTI	ILLETERATE	HW	YES	CPS	CBZ			13	NO	600			N0	NO	Normal	TERM	natural	O	1	N	7	8	2
26	MULTI	ILLETERATE	HW	YES	CPS	CBZ			15	NO	1000			N0	NO	Normal	TERM	ELSCS	O	2	N	2	8	2
24	MULTI	ILLETERATE	HW	YES	GTCS	PHT			16	NO	200			N0	NO	Normal	TERM	natural	2	2	N	7	8	2
27	MULTI	ILLETERATE	HW	YES	GTCS	PHT	SVP		22	NO	200	200		N0	NO	Normal	TERM	natural	2	2	N	6	8	2
28	MULTI	ILLETERATE	HW	YES	GTCS	PHT			24	NO	300			N0	NO	Normal	PRETERM	natural	O	2	N	6	8	2
33	MULTI	ILLETERATE	HW	YES	CPS	CBZ			12	NO	400			N0	NO	Normal	TERM	natural	2	1	N	7	8	2
25	MULTI	PRIMARY	HW	YES	GTCS	PHT	SVP	LEV	10	NO	100	400	1000	N0	NO	Normal	TERM	natural	O	2	N	2	7	2
29	PRIMI	ILLETERATE	HW	YES	GTCS	PHT			13	NO	200			N0	NO	Normal	TERM	natural	O	2	N	5	7	2
22	MULTI	ILLETERATE	HW	YES	GTCS	SVP			22	NO	400			N0	NO	Normal	PRETERM	natural	O	2	N	6	7	2
25	PRIMI	ILLETERATE	HW	YES	GTCS	PHT	SVP	LEV	20	NO	100	600	500	N0	NO	Normal	TERM	natural	O	2	N	5	7	2
23	PRIMI	PRIMARY	HW	YES	GTCS	PHT			14	NO	200			N0	NO	Normal	TERM	natural	O	1	N	5	7	2
26	PRIMI	PRIMARY	WORK	YES	GTCS	PHT			12	NO	200			N0	NO	Normal	TERM	natural	O	2	N	5	7	2
32	MULTI	PRIMARY	HW	YES	CPS	CBZ			12	NO	400			N0	NO	Normal	PRETERM	natural	2	2	N	6	8	2
20	PRIMI	PRIMARY	HW	YES	GTCS	PHT	CBZ		12	NO	400	200		N0	NO	Normal	TERM	natural	O	2	N	6	8	2
27	MULTI	PRIMARY	HW	YES	GTCS	PHT			12	NO	200			N0	NO	Normal	TERM	natural	O	2	N	6	8	2
33	PRIMI	PRIMARY	HW	YES	GTCS	PHT	SVP		12	NO	200	400		N0	NO	Normal	PRETERM	natural	O	2	N	7	9	2
31	PRIMI	PRIMARY	HW	YES	GTCS	PHT			12	NO	200			N0	NO	Normal	TERM	natural	O	2	N	7	9	2
26	PRIMI	PRIMARY	HW	YES	GTCS	SVP			12	NO	200			N0	NO	Normal	PRETERM	natural	O	1	N	6	8	2
25	PRIMI	PRIMARY	HW	YES	GTCS	PHT			10	NO	200			N0	NO	Normal	TERM	natural	O	2	N	6	8	2
23	MULTI	ILLETERATE	HW	YES	SPWSG	PHT			14	NO	200			NO	NO	Normal	TERM	natural	1	7	N	8	9	2

KEYS FOR MASTER CHART

POSTPARTUM PERIOD

1 - PPH

2 - SEIZURES

0 - NO COMPLICATIONS

BWT (BIRTH WEIGHT)

1 - <2.5KG

2 - >2.5KG

CM (CONGENITAL MALFORMATIONS)

1 - YES

2 - NO

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE. CHENNAI -3

Telephone No : 04425305301
Fax : 04425363970

CERTIFICATE OF APPROVAL

To
Dr. N. Thamilpavai
PG in DM Neurology
Madras Medical College, Chennai -3

Dear Dr. N. Thamilpavai

The Institutional Ethics Committee of Madras Medical College reviewed and discussed Your application for approval of the proposal entitled "The Impact of Epilepsy of the maternal and foetal outcome" No. 23032012.

The following members of Ethics Committee were present in the meeting held on 27.09.2011 conducted at Madras Medical College, Chennai -3

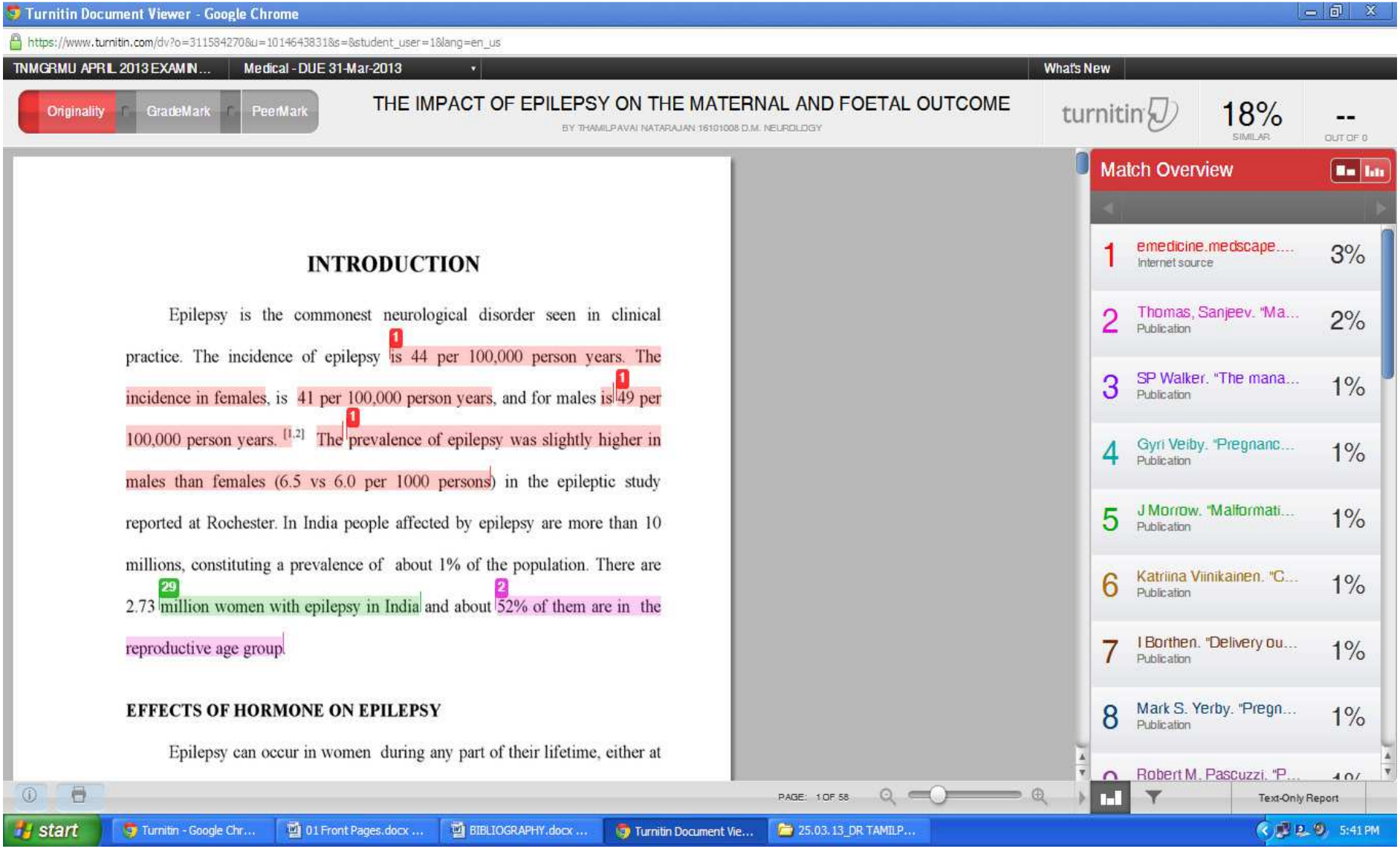
1.	Dr. S.K. Rajan MD	-- Chairperson
2.	Dr. V. Kanagasabai MD Dean, Madras Medical College, Chennai -3	-- Deputy Chairman
3.	Prof. R. Sundaram MD Vice Principal, Madras Medical College, Chennai -3	--Member Secretary
4.	Prof. R. Nandhini MD Director, Inst. Of Pharmacology, M M C, Ch -3	-- Member
5.	Prof. Pregna B. Dolia MD Director , Inst. of Biochemistry, M M C, Ch -3	-- Member
6.	Thiru . Ulaganathan Administrative Officer, M M C, Ch -3	-- layperson
7.	Thiru. S. Govindasamy BA BL	-- Lawyer
8.	Tmt. Arnold saulina .MA., MSW	-- Social Scientist

We approve the Proposal to be conducted in this presented from

Sd/ Chairman & Other Members

The institutional Ethics Committee expects to be informed about the progress of the study, Any SAE occurring in the course of the study , any change in the protocol and patient information / informed consent and asks to be provided a copy of the final report.

Member Secretary, Ethics committee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INTRODUCTION
Epilepsy is the commonest neurological disorder seen in clinical practice. The incidence of epilepsy is 44 per 100,000 person years. The incidence in females, is 41 per 100,000 person years, and for males is 49 per 100,000 person years. [1,2] The prevalence of epilepsy was slightly higher in males than females (6.5 vs 6.0 per 1000 persons) in the epileptic study reported at Rochester. In India people affected by epilepsy are more than 10 millions, constituting a prevalence of about 1% of the population. There are 2.73 million women with epilepsy in India and about 52% of them are in the reproductive age group.
EFFECTS OF HORMONE ON EPILEPSY
Epilepsy can occur in women during any part of their lifetime, either at
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INTRODUCTION Epilepsy is the commonest neurological disorder seen in clinical practice. The incidence of epilepsy is 44 per 100,000 person years. The incidence in females, is 41 per 100,000 person years, and for males is 49 per 100,000 person years. [1,2] The prevalence of epilepsy was slightly higher in males than females (6.5 vs 6.0 per 1000 persons) in the epileptic study reported at Rochester. In India people affected by epilepsy are more than 10 millions, constituting a prevalence of about 1% of the population. There are 2.73 million women with epilepsy in India and about 52% of them are in the reproductive age group. EFFECTS OF HORMONE ON EPILEPSY Epilepsy can occur in women during any...